PHTHALIC ACID ESTERS

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PREFACE

The preparation of this biblographic review or "toxifile" on phthalic acid esters (PAEs) was undertaken as part of the programme to assess the environmental and health impact of chemicals, as required by the Environmental Contaminants Act.

The format adopted for this report is intended to give comprehensive coverage of topics related to the assessment of human health effects while allowing inclusion of new information as it becomes available.

Data described in this toxifile have been drawn not only from many research papers but also from review articles and reports (Thomas, 1977?; Leah, 1977; Leah, 1975?; Peakall, 1975: Autian 1973; and Hugos, 1972a) as well as from papers presented at a conference on PAEs, sponsored by the (U.S.) National Institute of Environmental Health Scientists (NIEHS), Pinehurst, North Carolina, September 6 and 7, 1972 (Anon., 1973a) and from papers presented at a Regional Technical Conference of the Society of Plastics Engineers, Inc. on Flexible Vinyls and Human Safety: An Objective Analysis, Kiamesha Lake, N.Y., March 20 to 22 1973 (Anon., 1973b).

A computer search of the relevant literature by the National Health and Welfare Library was completed on June 3, 1978. Further references (to early 1977) but not all of those located in that search, were obtained from another computer search done at the Canada Centre for Scientific and Technical Information (CISTI).

This report was prepared by the Bureau of Chemical Hazards, Environmental Health Directorate, Health Protection Branch, Department of National Health and Welfare. The principal author, Dr. J.W.S. Jamieson, acknowledges the assistance of Dr. V.C. Armstrong, Dr. D.C. Villeneuve, Dr. Ih Chu, and Dr. G.R. Douglas for helpful discussions during the preparation of this report and for reviewing some or all of its sections. Provision of much reference material by the Contaminants Control Branch, Environmental Impact Control Directorate, Environment Canada is also appreciated.

SUMMARY

Phthalic acid esters or esters of 1,2-benzenedicarboxylic acid $C_6H_4(COOH)_2$ are prepared by reacting either phthalic acid or phthalic anhydride with various specific alcohols. Some common phthalate esters are: dimethyl phthalate, diethyl phthalate, dibutyl phthalate (DBP), dihexyl phthalate, and di-(2-ethylhexyl) phthalate (DEHP). Most of the phthalate esters are colourless liquids of medium viscosity which have very high boiling points and very low vapour pressures.

Analytical determination of phthalate esters is usually done by integrated gas-liquid chromatography-mass spectrometry (GLC-MS). The current detection limit by GLC is approximately 10 ng.

Phthalate esters are used mainly as plasticizers for resins and polymers such as polyvinyl chloride (PVC). In 1973, 27 900 tonnes of phthalate esters were manufactured in Canada and 7700 tonnes were imported. More than 95 percent of the total quantity was used in PVC resins. The most widely used phthalate plasticizer is di-(2-ethylhexyl) phthalate (DEHP). Other applications accounted for only 0.9 percent of Canadian demand in 1973 and included the use of phthalates in cosmetics, rubbing alcohol and insect repellant.

The occurrence of phthalate esters in the environment is ubiquitous. They have been found in various countries in water (raw and finished drinking water, rainwater, river, lake and ocean water); in aquatic sediments; in ambient air and in the air of automobiles, spacecraft, shipboard living quarters, and mobile homes; in many foods; in animals (including cattle, rabbits, rats, dogs and cockroaches); in various aquatic organisms; in naturally occurring rock bitumenoids (coals), shale and crude oil, tobacco leaves, several families of fungi, and many other plants; in almost all common laboratory equipment and reagents; and in human blood and tissue. Substantial quantities of phthalate esters have been found in the effluent of PVC plastic production and processing plants. The large quantities of plastic materials in solid wastes result in leaching of phthalate esters from landfill sites and emission of phthalate esters from municipal incinerators.

Substantial bioaccumulation of phthalate esters has been observed in the mosquito, the alga, the snail, and in various aquatic species.

Biodegradation appears to be the best method for effectively controlling pollution by phthalate esters in industrial effluents.

There appears to be no evidence that phthalate esters are in any way essential for nutrition or that they have any particular biological role.

Phthalate esters are readily absorbed by mammals through the lungs, skin or gastrointestinal tract. They accumulate temporarily in the liver but they are rapidly metabolised and excreted.

The acute toxicity of phthalate esters is low. Phthalate esters have also been found to have very low chronic toxicity. High doses of some phthalate esters have been found to be mutagenic and teratogenic in laboratory animals. Oral doses of phthalate esters have caused decreased fertility in mice and testicular degeneration in rats. There appears to be no evidence that phthalates are carcinogenic.

Phthalate esters have been found in Canada at concentrations as high as 9 µg/L in drinking water, approximately 1 µg/m^3 in air, and 0.24 µg/g (on a wet weight basis) in the most contaminated fish samples available to the Canadian consumer. On the basis of a worst-case estimate, the maximum daily intake of phthalate esters by man from food, air and water would be 0.23 mg.

There appears to be no appreciable risk to the general public from the levels currently occurring in the Canadian environment, since the resulting degree of exposure is well below that generally believed to be toxic.

Note added in press: The results of a two-year study conducted by the United States National Cancer Institute, which were released recently by the U.S. Environmental Protection Agency, were interpreted as showing that di-(2-ethylhexyl) phthalate caused liver cancer in rats and mice. Currently, these results are being evaluated by staff of the Health Protection Branch, Department of National Health and Welfare; if the findings are confirmed, reappraisal of the health risks associated with exposure to phthalic acid esters may be warranted.

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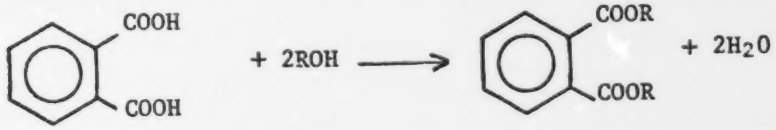
I. INFORMATION DATA BANK

I. INFORMATION - DATA BANK

A. IDENTITY, PROPERTIES AND ANALYSIS

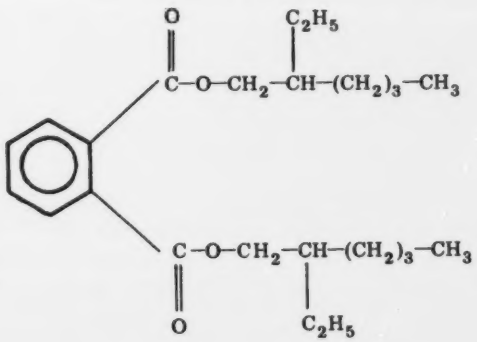
1. Chemical Identity

Phthalic acid esters (PAEs) are esters of 1,2-benzenedicarboxylic acid. They may be called phthalate esters or phthalates although the latter term is also used for salts of phthalic acid. A desired phthalate ester may be prepared by reacting phthalic acid with the appropriate alcohol, as follows:



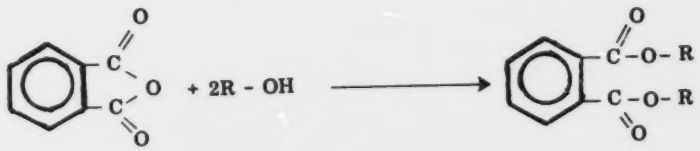
R = alkyl group

The molecular weight of phthalic acid ($C_8H_6O_2$) is 166.14. One of the most commonly used phthalate esters is di-(2-ethylhexyl) phthalate (DEHP) which



Di-2-ethylhexyl phthalate (DEHP)

has a molecular weight of 391.0. In the industrial production of phthalate esters, phthalic anhydride, rather than the acid, is normally used (Leah, 1977).



R = 2-Ethylhexyl

One of the commonly used industrial plasticizers is Dialkyl 79 Phthalate. This is a mixture of phthalate esters made from alcohols having carbon chains of 7 to 9 atoms (Autian, 1973).

Econol ® is a proprietary formulation, of the General Electric Company, which contains a phthalate ester base liquid and has been specially purified and stabilized for use as an impregnant for a-c capacitors (Goldy and Solberg, 1975).

2. Physical Properties

Most of the phthalate esters are colourless liquids of medium viscosity which have very high boiling points and very low vapour pressures (Patty, 1967; Fishbein and Albro, 1972; Autian, 1973). The low vapour pressures are important in contributing to their general stability in plastics (Patty, 1967; Fishbein and Albro, 1972). Temperature-vapour pressure relationships for some phthalates are shown in Table 1 and some other properties of phthalate esters are shown in Table 2, 3 and 4.

TABLE 1

Temperature-Vapour Pressure Data for Some Phthalates

	Temperature, °C, at Vapor Pressures of	
	5×10^{-8} mm Hg	5×10^{-6} mm Hg
Di-n-octyl phthalate	82	132
n-Octyl n-decyl phthalate	80	138
Diisooctyl phthalate	72	121
Di-2-ethylhexyl phthalate	68	120
Di-n-hexyl phthalate	54	120

These data are from Gross and Colony (1973).

TABLE 2

Same Properties of Phthalate Esters

Compound	Molecular Weight	Specific Gravity	BP, °C	Solubility in H_2O, g/100 mL
Dimethyl phthalate	194.18	1.189(25/25)	282	0.5
Diethyl phthalate	222.23	1.123(25/4)	296.1	Insoluble
Diallyl phthalate	246.27	1.120(20/20)	290	0.01
Diisobutyl phthalate	278.3	1.040	327	Insoluble
Dibutyl phthalate	278.34	1.0465(21)	340	0.45(25°C)
Dimethoxyethyl phthalate	282.0	1.171(20)	190-210	0.85
Dicyclohexyl phthalate	330.0	1.20(25/25)	220-228	Insoluble
Butyl octyl phthalate	334.0	-	340	-
Dihexyl phthalate	334.0	0.990	-	Insoluble
Butylphthalyl butyl glycolate	366.37	1.097(25/25)	219/5 mm/	0.012%
Dibutoxyethyl ethyl phthalate	366.0	1.063	210	0.03
Di-2-ethylhexyl phthalate	391.0	0.985(20/20)	386.9/5 mm	Insoluble
Diisooctyl phthalate	391.0	0.981	239/5 mm	Insoluble
Di-n-octyl phthalate	391.0	0.978	220/5 mm/	Insoluble
Dinonyl phthalate	419.0	0.965	413	Insoluble

These data are from Patty (1967) and Autian (1973).

TABLE 3

Other Properties of Phthalate Esters

Phthalate Ester	Boiling Point (°C)	Vapor Pressure (mm Hg)[a] 150°C	200°C	250°C	Solubility in Water (g/100 mL)
Dicyclohexyl	220-228	<0.1	1.5	20.0	<0.010 (25°C)
Dibutyl	340	0.8	14.0	100.0	0.001 (30°C) 0.450 (25°C)
Diethyl	296	6.3	55.0	260.0	0.100 (32°C)
Diisodecyl	256[b]	-	1.1	8.0	<0.005 (25°C)
Di(2-ethylhexyl)	387[c]	-	1.2	18.0	0.005 (25°C)
Dimethyl	282	13.0	91.0	360.0	0.400 (32°C)

[a]Monsanto Chemical Co. Data Sheets.
[b]Ten mm Hg.
[c]Five mm Hg.

These data are from Peakall (1975).

TABLE 4

Electrical and Physical Properties of Phthalate Esters

Phthalate	Di-2-ethylhexyl	Diisononyl
Dielectric Constant	5.33	4.66
Tangent Delta (%)	0.14	0.05
A-C Conductivity 10^{-11}(ohm-cm)$^{-1}$	2.1	0.29
Breakdown Voltage MV/m	11.0	11.8
Boiling point mid @ 5mm Hg. °C	230	252
Pour Point, °C	-50	-48
Viscosity, cps., 20°C	81	95
Flash Point, COC, °C	218	221
Fire Point, COC, °C	246	257

These data are from Ross and Schirn (1978).

The viscosity of di-(2-ethylhexyl) phthalate has been measured as a function of pressure by Mclachlan (1976) with the use of a new high pressure viscometer which consisted essentially of a high pressure linear variable differential transformer (LVDT) to detect the free fall of an unguided cylinder with a coaxial hole. Results at 30°C ranged from 4.5 Pa s at a pressure of 254 MPa to 2.9 x 10^2 Pa at a pressure of 550 MPa. The maximum difference between these results and those obtained using an established technique (Irving and Barlow, 1971) was found to be less than $\pm$ 3 percent.

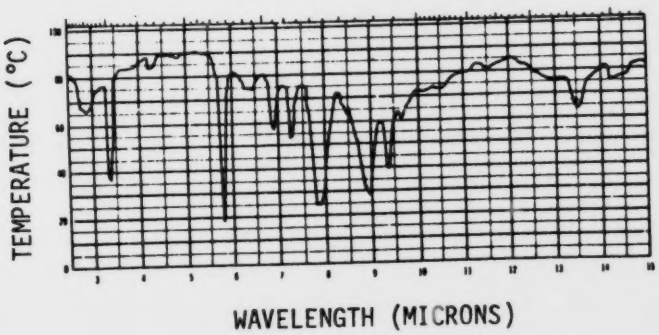
The infrared spectrum and the nuclear magnetic resonance spectrum of di-(2-ethylhexyl) phthalate have been described by Nazir et al. (1973 as follows:

The infrared spectrum (Figure 1) showed a band at 13.5 μ, indicating the presence of an ortho-disubstituted benzene ring. Absorption bands at 7.9 , 8.9, and 9.4 μ were attributed to carbon-oxygen absorption which is characteristic of phthalates. The band at 5.8 μ was attributed to the ester carbonyl, the band at 6.9 μ to the aliphatic C-H, and the band at 7.3 μ to the methyl groups.

The nuclear magnetic resonance (NMR) spectrum (Figure 2) showed a pair of overlapping triplets centered about 9.1, overlapping multiplets with the strongest peak at 8.7, a doublet at 5.9, and another multiplet centered at 2.5. The chemical shifts have been expressed in parts per million (ppm) relative to tetramethyl silane at 10 ppm (τ scale).

FIGURE 1

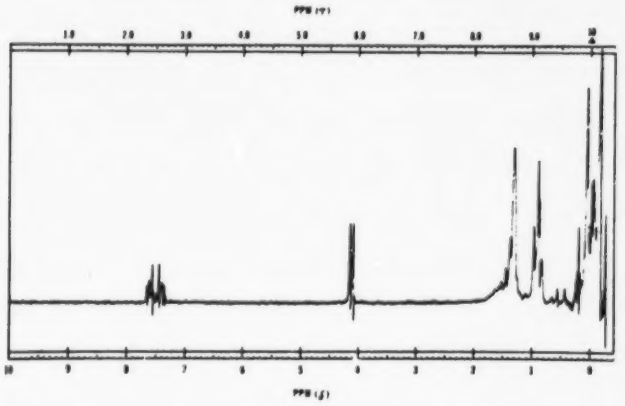
Infrared Spectrum of Di-(2-ethylhexyl) Phthalate



From Nazir et al. (1973).

FIGURE 2

NMR Spectrum of Di-(2-ethylhexyl) Phthalate



from Nazir et al. (1973).

3. Solubilities

Slightly different solubilities which have been reported for various phthalate esters are shown in Tables 2 and 3 (Section A.2). Fishbein and Albro (1972) have reported the solubility of di-(2-ethylhexyl) phthalate (DEHP) to be 0.01 g/100 g of water, which is twice the solubility given in Table 3. Fukano and Obata (1976) have recently reported some other aqueous solubility values at 25°C for some typical phthalates, as follows:

dimethyl phthalate	45 000 ppm (4.5 g/100 g)
diethyl phthalate	1 200 ppm (0.12 g/100 g)
dibutyl phthalate	13 ppm (0.0013 g/100 g)

These solubilities were measured by a new method which consisted of separation of the excess ester by centrifugation to leave a saturated aqueous solution, followed by hexane extraction of the ester from the water and determination of the ester by gas-liquid chromatography (GLC).

4. Chemical Properties

Phthalates, in sulphuric acid, react with phenol to form phenolphthalein. This reaction may be used for quantitative analysis of phthalate esters, since phenolphthalein can be determined spectrophotometrically (Rapaport et al., 1972).

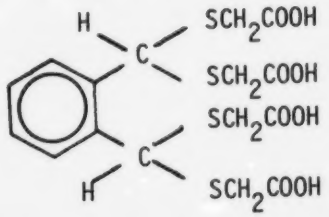
Hutzinger et al. (1973) investigated the exhaustive chlorination (perchlorination) of various aromatic compounds. They did not obtain well-defined chloro derivatives of either dibutyl phthalate or dihexyl phthalate. Partial hydrolysis of the ester linkage probably occurred. Kodama and Takai (1974d) have reported that chlorine had no effect on dibutyl phthalate other than the formation of mono - or di-chloro substituted dibutyl phthalate only when treated with high concentrations of chlorine at high temperature for long periods of time.

It has been shown by Brodman et al. (1976) that all of eleven phthalate esters studied formed hydrogen bonds with nitrocellulose. The interaction was found to be between the carbonyl groups of each phthalate ester and the unesterified hydroxyl groups in nitrocellulose.

The radical copolymerization of methylallyl benzoate with diallyl phthalate (and with diallyl isophthalate and diallyl terephthalate) using benzoyl peroxide as initiator, has been studied by Matsumoto et al. (1973).

Ogner and Schnitzer (1970) and Matsuda and Schnitzer (1971) have shown that dialkyl phthalates can form complexes with fulvic acid (which is usually found in humic substances in soils and waters).

Phthalyltetrathioacetic acid (PTTA) has been synthesized by Jones (1974). It has the following structure.



This compound is potentially an octadentate ligand; it has four sulphur donors and four carboxylate donors, and these are useful for chelation of mercury (II) ions (Jones and Harbison, 1974).

5. Analytical Methods

(a) Extraction

Stalling et al. (1973, Sherma, 1975) extracted phthalates and their metabolic products from fish tissue. A sample of tissue was blended with anhydrous sodium sulphate, packed into a column, and extracted by percolation with one per cent phosphoric acid in acetone.

Phthalate esters from samples of human blood plasma dissolved in methanol-chloroform, with 2.5 mL of 0.75 percent NaCl solution added, were extracted with chloroform by Marcel (1973).

Corcoran (1973) and Zitko (1973) extracted phthalate esters from water samples with hexane. Kodama and Takai (1974a) used 150 mL of n-hexane to extract phthalates at concentrations in the ppb range from 3 L samples of water.

Katase and Kobayashi (1974) extracted phthalate esters from 5 mL of serum with 5 mL of hexane in the presence of 3.75 mL of acetonitrile and 1.25 mL of formic acid. The hexane layer was evaporated to dryness and the residue was dissolved in hexane prior to analysis. Average recoveries of dibutyl phthalate which had been added to serum were 45 percent of 2 ppm and 64 percent of 6 ppm.

Takeshita et al. (1975) used hexane to extract phthalate esters from biological and environmental samples.

Ueta et al. (1976) reported that dibutyl phthalate (4 µg/20 g) and di-(2-ethylhexyl) phthalate (4 µg/20 g) added to fish meat were extracted with 1:4 ether-hexane. The recoveries were 70.2 percent for dibutyl phthalate and 87.9 percent for di-(2-ethylhexyl) phthalate.

Tomita et al. (1977) separated phthalate esters from foodstuffs using ether extraction for samples of non-fatty foods or n-hexane-acetonitrile partitioning for samples of fatty foods.

(b) Cleanup

Mayer et al. (1972) extracted phthalate esters from fish samples and recovered them from a Florisil column in a petroleum ether eluate containing 15 percent of diethyl ether. The recovery of di-n-butyl phthalate was 90 percent and that of di-(2-ethylhexyl) phthalate was 50 percent.

Stalling et al. (1973) cleaned fish sample extracts containing phthalate esters by using either solvent partition or gel permeation chromatography, followed by column chromatography on Florisil.

Kodama and Takai (1974b) separated alkyl phthalates from chlorinated organic compounds such as DDT and pentachlorobiphenyl by column chromatography using a Florisil column. A hexane extract containing the phthalates and the organochlorine compounds was partitioned with acetonitrile to remove the lipid component, then chromatographed on Florisil using successively hexane, hexane containing 10 percent diethyl ether, and hexane containing 30 percent diethyl ether.

Kodama and Takai (1974d) also compared two methods for the separation of dibutyl phthalate and di-(2-ethylhexyl) phthalate from oil. Recovery of these phthalates was less than 90 percent by sweep codistillation cleanup but greater than 95 percent by column chromatography using Florisil as the solid phase and water containing acetonitrile as eluent.

Giam et al. (1975a) separated phthalate esters from various chlorinated hydrocarbons, which are normally present in marine biota samples, using column chromatography on deactivated Florisil (containing 3 percent water w/w).

Tomita et al. (1977) separated phthalate esters from other organic environmental contaminants by column chromatography on non-activated Florisil containing 2.5 to 3.0 percent water. Chlorinated pesticides and polychlorinated biphenyls (PCBs) could be eluted with 100 mL of 4 percent diethyl ether in n-hexane and all phthalate esters with 100 mL of 3 percent acetone in n-hexane.

Columns of silica gel, alumina, celite, and activated charcoal have also been used for cleanup of phthalates but all of these require more than twice the elution time of a Florisil column (Kodama and Takai, 1974d).

(c) Gas Chromatography

Gas-liquid chromatography (GLC) more than any other method, has been used for determination of phthalate esters. A summary of some conditions used by various scientists for this purpose is shown in Table 5. One of the best separations of phthalate esters yet reported is that published by Tomita et al. (1977), which is shown in Figure 3. Tomita et al. (1977) were evidently able to detect less than 10 ng of various phthalates and less than 1 ng of n-butylphthalyl-n-butyl glycolate (BPBG).

Mayer et al. (1972) reported detection limits of 0.1 µg/g for di-n-butyl phthalate and 0.05 µg/g for di-(2-ethylhexyl) phthalate. Kaneshima et al. (1974) reported that the limit of detection of phthalates by their gas-liquid chromatography method was 0.10 µg.

Giam et al. (1975a), as shown in Table 4, used either a ^{63}Ni electron capture detector in a d-c mode or a tritium electron capture detector in a pulse mode. With either detector about 5 ng of di-(2-ethylhexyl) phthalate gave 50 percent full scale deflection.

Yasuhira et al. (1975) have reported a detection limit of 0.1 ppm for phthalate esters by gas chromatography.

Giam et al. (1975b) reported the detection of ng/m^3 concentrations of phthalate esters (and of polychlorinated biphenyls) in air.

Ueta et al. (1976) reported recoveries and detection limits of 70.2 percent and 0.07 ppm for dibutyl phthalate and 87.9 percent and 0.05 ppm for di-(2-ethylhexyl) phthalate.

Internal standards have been used in gas-liquid chromatography. Roll et al. (1974) used di-n-octyl phthalate and Kaneshima et al. (1974) used methyl stearate.

TABLE 5

Summary of Some Conditions Used for Analysis of PAEs by Gas-Liquid Chromatography

Column	Injector Temp. °C	Column Temp. °C	Detector Temp. °C	Type of Detector	Reference
2% diethyleneglycol succinate (DEGS) 0.5% H_3PO_4 on Chromosorb W AW, DMCS	250	190 to 200	210		Tomita et al. (1977)
3% SE-30 on Gas-chrom Q	250	180	275	^{63}Ni EC (10 mCi)	Giam et al. (1976a)
5% OV-210 on Chromosorb W HP 5% OV-101 on Chromosorb W HP 10% SP-216-PS on Supelcoport	220 to 240	165 to 192	270	Flame Ionization	Williams and Blanchfield (1975)
3% SE-30 on Gas- Chrom Q	250	200	275	^{63}Ni EC (10 mCi)	Giam et al. (1975b)
3% SE-30 on Chromosorb W HP	200	200	300	^{63}Ni EC (15 mCi)	
1.5% SP-2250, 1.95% SP-2401 on Supelcon, AW, DCMS	210	195	210	^{3}H EC (300 mCi)	
2% OV-1 on Gas-Chrom Q		150			Takeshita et al. (1975)
10% OV-17 on Gas-Chrom Q 3% SE-30 on Gas-Chrom Q 1.5% SP-2250, 1.95% SP-2401 on Supelcon AW, DMCS	250	185 220	275	^{63}Ni EC (10 mCi) in d.c. mode ^{3}H EC (150 mCi) in a pulse mode	Giam et al. (1975a)
Silicone SE-30, OV-17		145 to 250 (7.5°/min)			Kaneshima et al. (1974)
2% OV-25, OV-7 or OV-210					Kurihara et al. (1974)

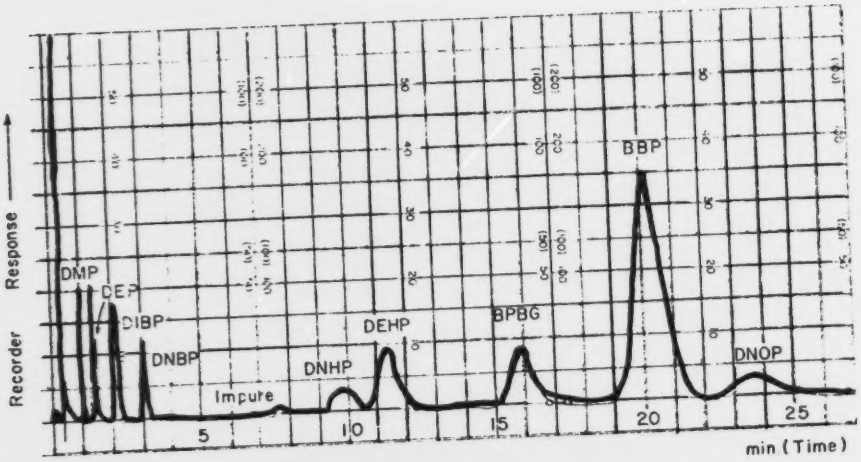
TABLE 5 (Cont'd)

Summary of Some Conditions Used for Analysis of PAEs by Gas-liquid Chromatography

Column	Injector Temp. °C	Column Temp. °C	Detector Temp. °C	Type of Detector	Reference
3% OV-210 on Chromosorb W HP	295	225	295	Flame Ionization	Roll *et al.* (1974)
3% SE-30 on Anakrom ABS	250	170 or 240	270	Flame Ionization	Zitko (1973)
1.5% OV-17, 1.95% QF-1 on Gas-Chrom Q		200	250	He arc emission EC	Corcoran (1973)
3% SE-30 (Ultraphase) on Chromosorb W AW, DMCS	230	210	225	EC	Thomas (1973)
A polar phase of diethylene glycol succinate (DEGS)		195			
A non-polar phase of dimethyl silicone gum		175 initially (20/min)		Hydrogen Flame	Marcel (1973)
A polar 16% diethylene glycol succinate (DEGS)		180			
A relatively non-polar 8% Apiezon L		200			Naxir *et al.* (1973)
A two-phase SE52/XE60 (2:1) 5% SE-30		200			
OV-11 (0.3% w/w) coated on Corning GLC-110		182			Stalling *et al.* (1973)

FIGURE 3

Gas-liquid Chromatographic Separation of Phthalate Esters



Chromatograph, Shimadzu GC-4A PFE, GC-4B PFE; column, 200-cm length x 3-mm i.d., packed with 2% DEGS-0.5% H_3PO_4 (Chromosorb W, AW-DMCS, 80/100); dimethylphthalate (DMP), diethyl phthalate (DEP), di-n-butylphthalate (DNBP), di-n-heptyl phthalate (DNHP), di-2-ethylhexyl phthalate (DEHP), n-butylphthalyl-n butyl glycolate (BPBG), n-butylbenzyl phthalate (BBP), di-n-octyl phthalate (DNOP); column temperature, 190 - 200°C; injection, 250°C, detector, 210°C; nitrogen carrier flow, 40 - 80 ml/min. All phthalic acid esters used in this experiment were 10 ng except BPBG (1 ng).

From Tomita et al. (1977)

(d) Mass Spectrometry

Many scientists have used mass spectrometry in combination with gas-liquid chromatography, particularly to confirm the identity of each substance detected as a peak in gas chromatography.

Hites (1973) noted that upon electron impact all phthalate esters (except dimethyl phthalate) produce a very abundant fragment ion at m/e 149 due to protonated phthalic anhydride. If the alkyl chain has six or more carbons, an ion of m/e 167 is also produced. For small alkyl chains (with four carbon atoms or less) ions at m/e 163, 177, 191 or 205 predominate instead of m/e 167. Other important fragment ions give peaks at m/e 223 for n = 4 and at m/e 279 for n = 8. Hites (1973) stated that molecular ions are usually of such low abundance that they are not observed. Mass spectra of dibutyl phthalate and di-(2-ethylhexyl) phthalate from river water samples were illustrated in the article by Hites (1973).

Thomas (1973) used an AEI MS-30 mass spectrometer with an electron bombardment ion source (24ev). The interface between the gas chromatograph and the mass spectrometer was of all-glass design utilizing a single-stage silicone molecular membrane, which was maintained at 195°C. The electron trap current was set at 400 μA and the source temperature was maintained at 230°C. By far the most intense ion in the mass spectra of all dialkyl phthalates other than dimethyl phthalate was the one at m/e 149 which was assumed to be a protonated anhydride even-electron ion. The spectrum of di-n-butyl phthalate had m/e 149 as the base peak, with peaks at m/e 223 and m/e 205 which each had a relative abundance of 5 percent. A molecular ion was present at m/e 278 plus a peak of small relative abundance at m/e 167. The spectrum of butyl-phthalyl butyl glycolate had m/e 149 as the base peak with a major peak at m/e 263 with a relative abundance of 41 percent. The spectrum of di-(2-ethylhexyl) phthalate had m/e 149 as the base peak, accompanied by others at m/e 167 and at m/e 279 with relative abundances of 23 and 10 percent, respectively.

Gross and Colony (1973) used combined gas chromatography and mass spectrometry with a computer interface. Results for di-(2-ethylhexyl) phthalate (DEHP) are shown in Table 6. Gross and Colony (1973) found the base peak at m/e 149 and other major peaks at m/e 167 and m/e 279 with relative abundances of 30.49 and 11.89 percent.

When Nazir et al. (1973) analysed various bovine heart muscle samples by gas-liquid chromatography a particular peak was consistently observed. The authors identified the compound which gave this GLC peak as di-(2-ethylhexyl) phthalate, using mass spectrometry and other methods. In the mass spectrum, the molecular ion $C_{24}H_{38}O_4^+$ gave a peak at the m/e value of 390.2765 rather than at the theoretical value of 390.2770. The m/e values of fragments with the highest relative abundance corresponded to rearrangement ions of phthalic anhydride (149; M-241); the diacid fragments (167; M-223); one derived by the loss of a 2-ethylhexyl group from the parent molecular ion (279; M-111); and a 2-ethylhexane hydrocarbon fragment (112; M-278).

According to Stalling et al. (1973) the characteristics of the electron impact mass spectra of phthalate esters permit ready identification of the esters as a group of compounds. The structure is indicated by the presence of a moderately intense ion corresponding to $(M-R + 2H)^+$ in the spectra of symmetrically substituted esters and an ion R^+ or $(R-H)^+$ corresponding to the alcohol moiety (Emery, 1960). For the higher esters, a very intense ion is observed at m/e^+ of 149 which corresponds to the protonated phthalic anhydride ion. No parent ion is generally observed with the higher alkyl esters by using electron impact mass spectrometry (Beynon et al., 1968). Stalling et al. (1973) used a PDP-12 LDP computer interfaced to a Perkin-Elmer Model 270-B gas-liquid chromatograph-mass spectrometer (GLC-MS) to record the mass spectra of dimethyl phthalate, di-(2-ethylhexyl) phthalate, and methyl n-butyl phthalate shown in Tables 7, 8, and 9. The mass spectrum of methyl 2-ethylhexyl phthalate was illustrated in the article by Stalling et al. (1973).

TABLE 6

DEHP Mass List, Computer/Teletype Presentation

```
MASS LIST
COMPUTER PRESENTATION
01 MTR, 470
02 MASCON
03 MTW
04 SUB, 470, 469
05 MLIST
06
RUN
BACKGROUND PEAKS MISSING
PEAKS   BCKGRND     70
6/1/71   /SPEC#  486/LM/
  BASE           SUM
 29031         248730
```

PEAK	INT	I/BASE	MASS	TEST
1	1466	5.04%	18	-1
3	2722	9.37%	27	-2
4	1730	5.95%	28	-2
5	6940	23.90%	29	-1
7	2499	8.60%	39	-2
9	12853	44.27%	41	-1
10	3405	11.72%	42	-1
11	14850	51.15%	43	-1
12	13404	46.17%	55	-1
17	5312	18.29%	56	-1
18	19597	67.50%	57	-3
19	1909	6.57%	68	-1
23	18904	65.11%	69	-0
24	15749	54.24%	70	0
25	3048	10.49%	75	3
28	4434	15.27%	83	-0
33	5227	18.00%	104	-1
39	5669	19.52%	112	-0
45	7904	27.22%	113	-0
46	29031	100.00%	149	-0
60	8852	30.49%	150	-0
61	21882	75.37%	167	-0
63	2499	8.60%	168	-0
75	3453	11.89%	279	0

These data are from Gross and Colony (1973).

TABLE 7

Mass Spectrum of Dimethyl Phthalate

Fragment Intensity Not Corrected for Changes in Sample Concentration During Scan

Peak	Mass	Intensity
9	32.10	18.26
10	44.09	2.11
11	50.10	10.05
12	51.09	1.52
13	52.10	2.11
14	62.80	1.12
15	63.90	2.44
16	65.89	2.18
17	74.00	1.58
18	75.00	3.63
19	75.89	10.78
20	76.89	20.38
21	78.00	1.52
22	79.10	2.05
23	92.00	9.92
24	104.20	1.12
25	105.00	4.10
26	119.90	2.58
27	128.70	1.12
28	133.00	5.62
29	135.00	7.80
30	163.00	100.00
31	163.90	13.76
32	165.00	2.38
33	194.00	9.26
34	195.00	2.18

These data are from Stalling *et al.* (1973).

TABLE 8

Mass Spectrum of Di-2-ethylhexyl Phthalate

Fragment Intensity Not Corrected for Changes in Sample Concentration During Scan

Peak	Mass	Intensity
10	41.19	21.79
11	42.20	4.47
12	43.20	27.43
13	44.20	6.76
14	50.10	.85
15	55.10	15.87
16	56.09	7.77
17	57.10	44.21
18	62.69	.85
19	64.89	2.02
20	67.40	.85
21	69.00	5.70
22	70.00	22.80
23	71.10	27.81
24	72.00	3.51
25	83.19	9.27
26	84.09	4.20
27	93.10	2.34
28	104.20	6.12
29	105.20	.85
30	112.19	9.27
31	113.30	13.53
32	121.20	2.02
33	112.20	1.86
34	132.10	2.77
35	135.10	2.45
36	144.20	.85
37	149.20	100.00
38	150.10	13.10
39	151.00	1.49
40	163.00	3.30
41	167.00	37.34
42	168.00	3.72
43	207.10	1.97
44	269.2	.85
45	279.0	9.90
46	280.0	2.50
47	281.0	1.65

These data are from Stalling et al. (1973).

TABLE 9

Spectrum of Methyl n-butyl Phthalate from *in vitro* Degradation of Di-n-butyl Phthalate by Male Channel Catfish

Peak	Mass	Intensity
1	17.20	18.83
2	18.10	7.62
3	20.10	13.45
4	27.10	9.86
5	28.10	13.45
6	29.10	28.25
7	40.10	8.96
8	41.20	22.42
9	45.10	20.62
10	57.00	8.96
11	76.10	15.69
12	77.19	13.45
13	92.00	13.45
14	104.10	9.41
15	135.00	12.10
16	149.00	67.71
17	163.00	100.00
18	165.00	10.76
19	181.20	8.96

These data are from Stalling *et al.* (1973).

(e) Improved Sensitivity

Kodama and Takai (1974a) converted phthalate esters into dimethyl phthalate for determination in the µg/mL range by gas-liquid chromatography and mass spectrometry. The phthalates in a condensed eluate of n-hexane containing 5 percent ethanol were saponified with alkaline potassium hydroxide, followed by methylation with N,N-dimethyl formamide dimethyl acetal to yield dimethyl phthalate.

Takeshita et al. (1975) have described a method for the gas chromatographic determination of total phthalates as di-trifluoroethyl phthalate. This compound is said to be highly sensitive to an electron capture detector. Phthalates were esterified with 2,2,2-trifluoroethanol in the presence of BF_3. The detection limit of di-(2,2,2-trifluoroethyl) phthalate was 0.1 pg and fatty samples fortified with phthalates at levels from 0.1 to 10 µg were successfully analysed with a recovery of 85 to 105 percent.

Giam et al. (1976a) converted phthalate esters into N-(2-chloroethyl) phthalimide for gas chromatographic analysis. The procedure involved hydrolysis of the esters followed by fusion of the resulting acid with 2-chloroethylamine hydrochloride to yield N-(2-chloroethyl phthalimide). This method gives a very low background of 20 ng or less of di-(2-ethylhexyl) phthalate and also yields the phthalimide free from most other compounds present in environmental samples. According to the authors, these factors, along with the high product yield of 90 percent, allow the method to be used for quantitative analysis of total phthalates as well as for confirmation of the individual phthalates.

(f) Analytical Problems

Tepper (1973) drew attention to the possibilities of extraneous sources of laboratory contamination and of misinterpretation and misidentification of gas chromatography peaks.

Hartung (1974) noted that some analytical results for phthalate esters have been erroneous, due probably to contamination (or cross-contamination). He recommended that blanks should be run through the full analytical procedures to account for possible impurities and for cross-contamination.

Belisle et al. (1975) used special precautions with respect to cleanliness of reagents and apparatus to reduce background levels of dibutyl phthalate and di-(2-ethylhexyl) phthalate from levels as high as 30 and 20 µg/g to ≤0.4 µg (sic) and ≤2.5 µg (sic), respectively.

Giam et al. (1975a) noted that various chlorinated hydrocarbons, which are normally present in marine biota samples, interfere with ECD-GC determination of phthalates. They were able, however, to separate these compounds by column chromatography on Florisil. Giam et al. (1975a) found that almost all equipment and reagents used in the laboratory contained di-(2-ethylhexyl) phthalate, as is shown in Table 10. With careful decontamination of all reagents and equipment used in the analytical procedure, background levels as low as 25 ng of dibutyl phthalate and 50 ng of di-(2-ethylhexyl) phthalate (DEHP) were obtained.

In a recent review article, Hartung (1976) noted that the major problem in analysing for phthalate esters was still contamination during sample preparation and from reagents.

Stalling et al. (1973) undertook investigations to establish which derivatives of phthalate ester metabolites are suitable for gas chromatographic analysis. The methyl and n-butyl 3-O-trifluoroacetyl phthalates and the trimethylsilyl derivative of 3-hydroxyphthalatic (sic) acid were examined. According to Stalling et al. (1973) only the trimethylsilyl derivative gave satisfactory peaks in gas chromatography.

(g) Other Methods of Analysis

Various methods, other than gas-liquid chromatography (GLC) or the combination of gas-liquid chromatography and mass spectrometry (GLC-MS), have been used either for direct analysis or confirmation of results obtained by other means.

Fishbein and Albro (1972) reviewed various analytical methods for phthalates including thin-layer chromatography and liquid-chromatography, as well as gas-liquid chromatography.

Rapaport et al. (1972) analysed for phthalate esters (from polyvinyl chloride materials) by reacting them in sulphuric acid with phenol to form phenolphthalein, which was then determined spectrophotometrically. Polyvinyl chloride and polyvinyl chloride additives did not interfere with the determination. The method detected less than 2 µg of phthalate and the relative error of the determination was $\pm$ 3 percent.

TABLE 10

DEHP Content of Some Common Laboratory Items

	ppb
Tygon tubing[a]	2×10^7
Neoprene stopper[a]	1.6×10^6
Black rubber tubing[a]	250 000
Black rubber stopper[a]	30 000
Cork[a]	6000
Amber latex tubing[a]	4000
Glasswool	1000
Polyethylene tubing[a]	800
Telfon sheet	400
Aluminum foil	300
Sodium sulfate	2
Sodium chloride	1.5
Tap water	1.5
Florisil	0.05
Blank	500-1000 ng

[a]Hexane content of 1-2 mm of "minced" material.

These data are from Giam et al. (1975a).

Nazir et al. (1973) used various methods including elemental analysis, carbon skeleton chromatography, infrared and nuclear magnetic resonance spectrometry, as well as mass spectrometry to confirm the presence of di-(2-ethylhexyl) phthalate in their samples.

Zitko (1973) achieved additional cleanup of phthalates by extracting them from hexane into dimethyl formamide. Phthalates could then be confirmed by measurement of their fluorescence in concentrated sulphuric acid. Approximately 0.06 µg of phthalates, expressed as di-(2-ethylhexyl) phthalate, could be detected in the presence of 100 ug of lipids. The detection limits of phthalates examined in this work were about 3 to 5 µg/g of lipid.

Kaneshima et al. (1974) determined dimethyl, diethyl, dibutyl, di-iso-butyl, di-n-octyl, and di-(2-ethylhexyl) phthalates by several different methods. Hexane extracts were analysed by silica gel thin-layer chromatography (4:1 n-hexane/diethyl ether, determined by $H_3PMo_{12}O_{40}$-anisaldehyde, limit of detection 0.2 to 0.5 µg), by thin-layer chromatography (fused silica gel on 9 x150 mm quartz rod, flame ionization detector, limit of detection 0.1 µg), or by gas chromatography.

Persiani and Cukor (1975) reported a simple liquid chromatographic method for the determination of phthalates in industrial and biological samples. A Waters Associates Model 202 liquid chromatograph equipped with a Model 6000 high-pressure pulseless liquid pump and a UV detector absorbing at 254 nm was used. Analyses were carried out on a one-foot long 10 µm Porasil polar column. Normal phase separation was used with 50 percent methylene chloride-50 percent isooctane as the mobile phase.

Hugos (1972b) and Sherma (1975) have published good reviews of analytical methods for phthalate esters.

B. PRIMARY OCCURRENCE, PRODUCTION, USE AND DISPOSAL

1. Geochemistry and Origin

The possible natural occurrence of phthalate esters has been considered by Graham (1973), Mathur (1974), Peakall (1975) and others (see below).

Klindukhov et al. (1974) have confirmed the presence of alkyl esters of phthalic acid in rock bitumenoids (coals) of different degrees of metamorphism. These phthalates were regarded by Klindukhov et al. to be related to the formation of light paraffinic petroleums. Phthalic acid has been found (Kokurin and Galutkina, 1967; Peakall, 1975) in shale and phthalic anhydride has been found (Breger, 1972; Peakall, 1975) in crude oil. Dioctylphthalate has been found (Phillips and Breger, 1958; Breger, 1966) to occur naturally in crude oil. According to the authors "reexamination with extreme care to prevent contamination proved that the ester is a true constituent of the oil".

There are probably other natural sources of PAEs. Phthalic acid has been found in poppies (Schmid and Karrer, 1945; Peakall, 1975). This determination was made before the use of phthalic acid and its esters became widespread. Phthalates have been found in olive oil and olive husk oil by Covello et al. (1967) and by Ranaudo and Schettino (1969) who considered the phthalates to be of natural origin. Phthalates have also been found in tobacco leaves (Swain et al., 1961). The authors thought that the presence of phthalates was not due to contamination as a result of the procedure used. Phthalic acid and various phthalates have been found in several families of fungi (Peakall, 1975).

2. Production, Imports and Exports

(a) Production

Leah discussed production, imports, and exports of phthalate esters in a recent report (Leah, 1977). He noted that the main source of data presented in his report (after the first three chapters) was a report (Anon., no date) by Corpus Publishers Services, Toronto, under contract to the Inland Waters Directorate, Ontario Region, in which a detailed analysis of production and use of phthalates was made. Leah (1977) stated that some information was obtained from government sources, primarily Statistics Canada.

According to Leah (1977), in 1973 a total quantity of 28 000 tonnes of phthalate esters, or 11 000 tonnes PAQ*, was manufactured in Canada. The only Canadian producers were: Carlew Chemicals, Montréal, Québec; Monsanto, Montréal, Québec, Badische Anilin und Soda Fabrik (BASF), Cornwall, Ontario; and Canadian General Electric, Toronto, Ontario. No current or more recent data regarding the production of phthalate esters in Canada are available from either the Department of Industry, Trade and Commerce or Statistics Canada.

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*PAQ = Phthalic Acid Equivalent, the amount of phthalic acid which is made from or is required to make the indicated amount of phthalate, phthalic anhydride, etc.

(b) Imports

The quantity of phthalates and phthalate esters* imported during 1977 was 2918 tonnes (Anon., 1978), which was very much less than the quantity of 24 400 tonnes reported by Statistics Canada as imported in 1973. Leah (1977) reported that 7700 tonnes of phthalate esters (or, including terephthalates, 25 700 tonnes) were imported in 1973.

Import data for the years 1968 to 1977 as shown in Figure 4 have been obtained from Statistics Canada. There seems to be no obvious explanation of the observed variation of quantities imported during those ten years. It is, however, apparent that the importation of phthalic anhydride has declined steadily since 1974 and that the importation of phthalates and phthalate esters has declined sharply since 1972. The total quantities of these substances imported have also declined markedly since 1972. The actual reasons for the importation of smaller quantities in recent years are not apparent. It is possible that larger quantities are now being manufactured in Canada, that other materials may be replacing phthalates as the major plasticizers for vinyl chloride resins, or that Canadian companies may be currently using stocks of phthalates imported previously.

Leah (1977) noted that, in 1973, apart from the 7700 tonnes of phthalate esters imported as such there were about 5200 tonnes of phthalate esters (1800 tonnes PAQ) contained in imported vinyl compounds, film and sheet, as well as about 6400 tonnes of phthalate esters (2300 tonnes PAQ) contained in imported fabricated vinyls.

The supply and demand of phthalates for 1973 is shown in Table 11. Figure 5 is a flowchart which illustrates the use and distribution in the Canadian economy of phthalate esters and one of the starting materials, phthalic anhydride, for 1973. All quantities have been expressed in tonnes PAQ.

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* Described by Statistics Canada as phthalates and phthalate esters not elsewhere specified (NES).

FIGURE 4

Phthalates Imported, 1968 to 1977

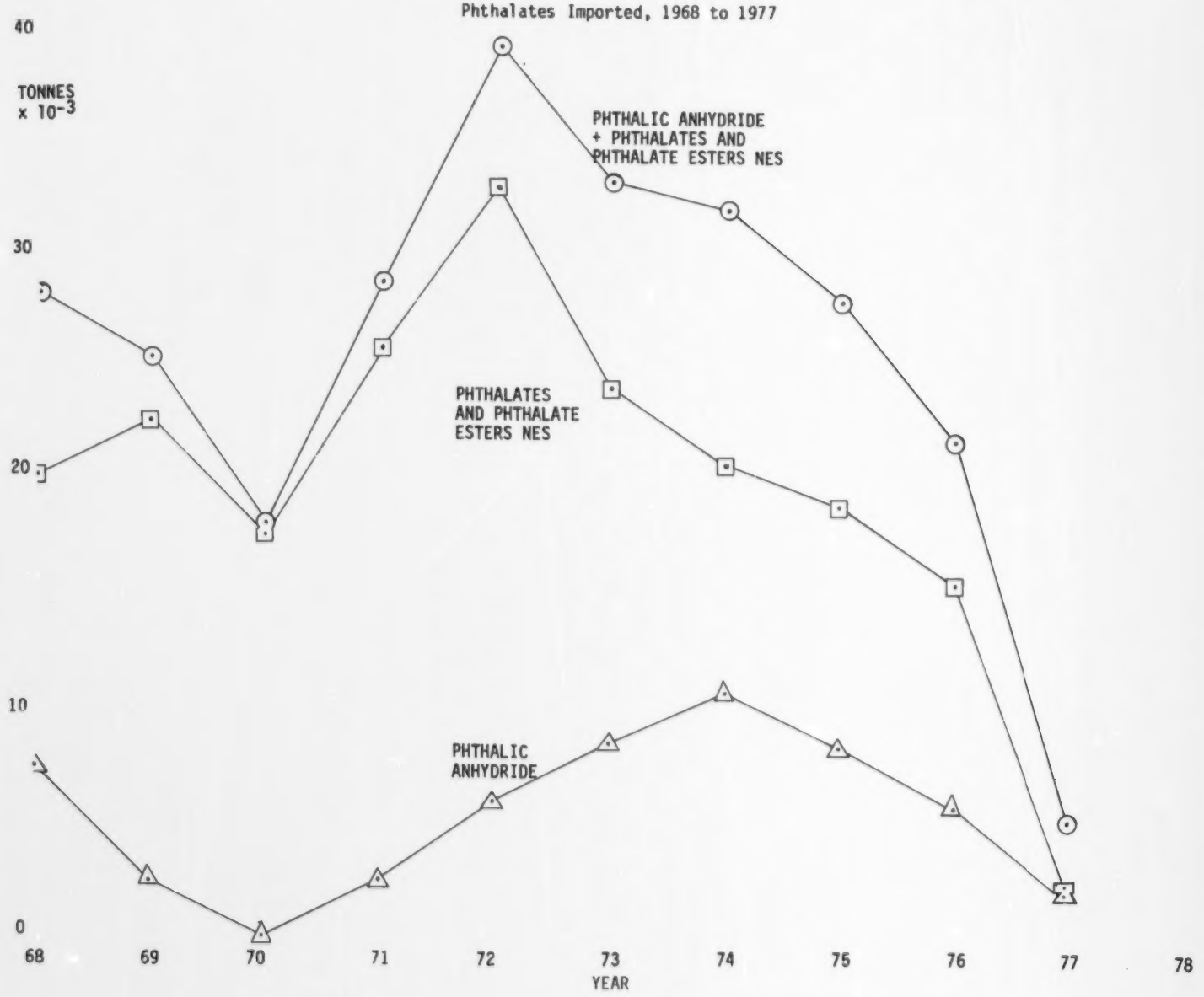


TABLE 11

Phthalates, Supply and Demand, 1973

	Phthalates (Tonnes)	PAQ (Tonnes)	Percent of Total
Supply			
Domestic production	27 900	10 800	78.3
Imports	7 700	3 600	21.7
Total	35 000	14 400	100.0
Demand			
(a) As plasticizers in:			
Plastisols	11 100	4 200	31.3
Extruded film and sheet	10 900	4 200	30.7
Flooring	5 800	3 000	16.3
Wire and cable insulation	4 700	1 800	13.2
Other vinyl extrusions and mouldings	2 000	770	5.7
Adhesives	230	90	0.6
Cellulose film coatings	230	140	0.6
(b) Other applications	320	140	0.9
(c) Export	230	90	0.6
Total	35 600	14 400	99.9

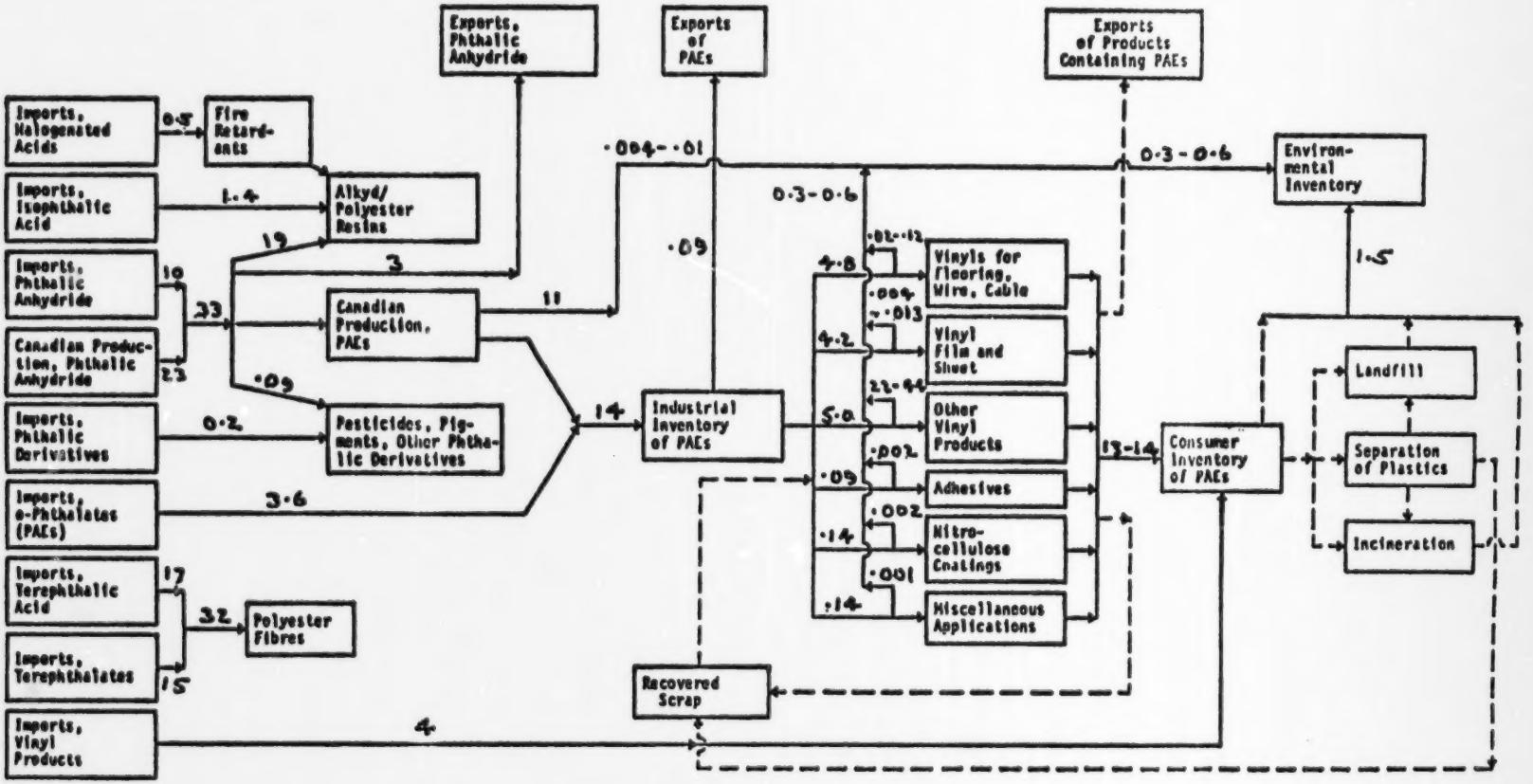
These data are from Leah (1977). Units have been converted from lbs. to tonnes.

Exports

Leah (1977) reported that about 230 tonnes of phthalate esters (ca. 90 tonnes PAQ) were exported during 1973.

FIGURE 5

Material Flowchart of Phthalic Anhydride and Phthalic Acid Esters (PAEs) in Canada, 1973 (tonnes, phthalic acid equivalent) x 10^{13}



Note: Dotted lines indicate unknown quantities.

These data are from Leah (1977). Units have been converted from lbs. to tonnes PAQ.

3. Uses and Users

Phthalate esters are used principally as plasticizers in polyvinyl chloride resins for plastisols, sheeting and film, flooring, and wire and cable insulation (as is shown in Table 11, page 29).

In 1973 at least 25 000 tonnes of PVC were used by the following Canadian formulators and consumers of plastisols: in Québec: Beckwith-Bemis Limited, Sherbrooke; Edmont (Canada) Limited, Cowansville; National Vintex Corp., Candiac; Stedfast Rubber Co. (Canada) Limited. Granby; British Rubber, Montréal; Crown Cork and Seal Co. Limited, Montréal; Daly and Morin Limited, Montréal; Dewey and Almy Chemical, Montréal; and Pervel Limited, Montréal; and in Ontario: Allen Industries (Canada) Limited, Hamilton; Barry Manufacturing Co. Ltd., Mississauga; Bata Industries Limited, Trenton; Biltrite Rubber (1969) Limited, Toronto; Carlaw Footwear, Toronto; Continental Can Co. of Canada Ltd., Toronto, Fortune Footwear, Hamilton; B.F. Goodrich (Canada) Limited, Kitchener; Kaufman Footwear Limited, Kitchener; M & T Products, Hamilton; Mobern, Cornwall; Rehau, Prescott; and W. R. Grace and Co. Limited, Mississauga (Leah, 1977). Leah (1977) estimated the consumption in 1973 of phthalate ester plasticizers for plastisols as about 11 100 tonnes (4200 tonnes PAQ) or, at least within the range from 10 000 to 18 000 tonnes. Included were 5670 tonnes (2130 tonnes PAQ) which were used in the manufacture of supported film.

In calendering and extrusion operations for the production of vinyl sheeting and film 19 000 to 20 000 tonnes of PVC resin and about 10 900 tonnes (4200 tonnes PAQ) of phthalate pasticizers were processed in 1973 by the following Canadian manufacturers: in Québec: B.F. Goodrich (Canada) Limited, Shawinigan; and Plastishaw, Shawinigan; and in Ontario: Monsanto, Oakville; Canadian General Tower Limited, Cambridge; Uniroyal Limited, Kitchener; Stauffer Chemical Co. of Canada Limited, Toronto; Borden Chemical Co. (Canada) Limited, West Hill; Goodyear Tire and Rubber Co. of Canada Limited, Toronto; TCF of Canada Limited, Cornwall; and Rubbermaid (Canada) Limited, Toronto (Leah, 1977).

In 1973 about 5800 tonnes of phthalate plasticizers (3000 tonnes PAQ) were used in the manufacture of vinyl floor tile and roll goods by the following Canadian companies: Flintkote Co. of Canada Limited, Toronto, Ontario; and American Biltrite Rubber Company (Canada) Ltd., Sherbrooke, Québec; Armstrong Cork (Canada) Limited, Montréal, Québec; and Domco Industries Limited, Farnham, Québec (Leah, 1977).

The production of wire and cable during 1973 consumed between 4540 and 4760 tonnes (ca. 1800 tonnes PAQ) of phthalate plasticizers. More than 85 percent of all Canadian wire and cable insulation was, in 1973, manufactured by the following companies: in Québec: Northern Electric, Montréal; Pirelli Cables Limited, St. Jean; ITT Wire and Cable, St. Jerome; and Rochevert Inc., Valleyfield; and in Ontario: Canada Wire and Cable Limited, Toronto; Philips Electronics Industries Limited, Brockville; General Wire and Cable Co. Limited, Cobourg; Alcan Wire and Cable, Bracebridge; Fabricon Manufacturing Limited, Trenton; Canadian General Electric, Peterborough; Industrial Wire and Cable (1970) Limited, Toronto; and Cable-Tech Wire Co. Limited, Stouffville (Leah, 1977).

In 1973, 6800 tonnes of plasticized PVC containing 2000 tonnes of phthalates (770 tonnes PAQ) were used in vinyl extrusion and injection moulding processes by at least the following companies: Rochevert Inc., Valleyfield, Québec; General Plastics Co. Limited, Cookshire, Québec; and Rehau, Prescott, Ontario (Leah 1977).

Approximately 230 tonnes of phthalate plasticizers were used in adhesive formulations in Canada in 1973. Some of the manufacturers were: Dural Products Limited, Dorval, Québec; and in Ontario: Polyresins Limited, Don Mills; Borden Chemical Co. Canada Limited, West Hill; Industrial Adhesives Limited, Toronto; Swift Chemical Company, Bramalea; Morgan Adhesives of Canada Limited, Brampton; and 3M Canada Limited, London (Leah, 1977).

According to Leah (1977) about 230 tonnes (Table 11, p. 29) of phthalate esters (ca. 140 tonnes PAQ), or as much as 180 tonnes of dibutyl phthalate (DBP) and 120 tonnes of dicyclohexyl phthalate (DCHP) were used in Canada in 1973 to coat nitrocellulose film to reduce water vapour transmission. This coated nitrocellulose film was manufactured by at least Du Pont of Canada Limited, Montréal, Québec and TCF of Canada Limited, Cornwall, Ontario (Leah, 1977).

Miscellaneous applications consumed about 320 tonnes of phthalate esters (ca. 140 tonnes PAQ) in 1973 (Leah, 1977). Some of these applications were the following:

(a) diethyl phthalate (DEP) in insect repellant formulations;

(b) dimethyl phthalate (DMP) as a defoaming agent in the manufacture of paper and paperboard;

(c) DEP to denature ethyl alcohol for use in cosmetics, perfumes, rubbing alcohol, liquid soap and detergents;

(d) dibutyl phthalate (DBP) in inks for decorative packaging;

(e) dioctyl phthalate (DOP) and DBP in laquers for industrial flooring and for applying phosphor to fluorescent lamps;

(f) DEP and DBP as cooling agents in military propellants;

(g) DMP as a carrier for peroxide catalysts in the production of polyester fibreglass reinforced plastics;

(h) phthalates as additives in industrial and lubricating oils, and

(i) the declining (because of cost) use of phthalates as carriers in pesticide formulations (Leah, 1977).

Recently, the use of diisononyl phthalate and di-(2-ethylhexyl) phthalate, instead of the polychlorinated biphenyls, as dielectrics in capacitors has been reported (Ross and Shirn, 1978; cf. Goldy and Solberg, 1975).
Apparently the fire hazard due to this use of phthalates can be minimized by incorporation of effective fuses in the capacitors.

4. Disposal of Wastes

Estimates, many of which were based on assumptions, of the quantities of phthalate esters released to the Canadian environment have been made in a recent report (Leah, 1977).

In 1973, Canadian releases of phthalate esters from production, processing, use, and disposal activities totalled between 4500 and 5400 tonnes (1700 to 2000 tonnes PAQ). Approximately 22 per cent of this total originated with production and processing activities. In the Southern Ontario basin about 38 percent and in the Mid-St. Lawrence basin about 35 percent of the total releases resulted from production and processing activities. In all other drainage basins in Canada virtually all releases resulted from use and disposal activities.

Production and processing activities in 1973 released between 718 and 1599 tonnes of phthalate esters (273 to 610 tonnes PAQ) as shown in Table 12. Releases of phthalate esters from production and processing activities into the Southern Ontario drainage basin are shown in Table 13.

Quantities of phthalate esters released to the environment at the consumer level within each of the main Canadian drainage basins are shown in Table 14.

Some information on quantities of phthalate esters released from incineration is shown in Table 15.

TABLE 12

Releases of PAEs from Production and Processing Activities, 1973 (tonnes)

	Release[1]	
Activity	As PAEs	As PAQ[2]
PAE Production	28 to 84	11 to 32
PVC Compounding and Processing		
Compounds preparation	19	7
Flooring products processing	58 to 295	23 to 113
Sheet and film, calendered/extruded	11 to 33	4 to 13
Wire and cable extrusion	5 to 10	2 to 4
Plastisols	583 to 1145	220 to 435
Other vinyl extrusion and moulding	2	1
Other		
Adhesives formulating	5	2
Cellulose film coating	3	2
Miscellaneous	3	1
Total	718 to 1599	273 to 610

[1]All figures rounded to the nearest tonne.

[2]Phthalic acid equivalent.

These data are from Leah (1977). Units have been converted from lbs. to tonnes.

TABLE 13

Releases of PAEs from Production and Processing Activities by Drainage Basin, 1973 (tonnes PAQ)

Activity	Releases		
	Southern Ontario Drainage Basin	Mid-St. Lawrence Drainage Basin	Total, Canada
Production of PAEs	*	*	11 to 32
PVC Compounding and Processing			
Compounds preparation	*	*	7
Flooring products processing	*		23 to 113
Sheet and films, calendered/extruded	3 to 10	1 to 3	4 to 13
Wire and cable extrusion	1 to 2	1	2 to 3
Plastisols	157 to 312	62 to 124	220 to 435
Other vinyl extrusion and moulding	0.1	1	1
Other			
Adhesive formulating	1	1	2
Cellulose film coating	2	-	2
Miscellaneous	0.6	0.6	1.2
Total	176 to 359 (268)+	96 to 251 (173)+	273 to 609

*Confidential.

+These figures are the simple averages of the maximum and minimum estimated releases.

These data are from Leah (1977). Units have been converted from lbs. to tonnes.

TABLE 14

Releases of PAEs from Use and Disposal Activities by Drainage Basin, 1973 (tonnes)

Basin	1971 Population[1] (000)	% of total Population	Approximate PAE Content of Residential, Commercial and Non-specific Industrial Wastes (tonnes)		
			Urban	Rural	Total
1. Fraser	1 395	6.5	221.5	29.6	251.1
2. Okanagan-Skagit	101	0.5	9.9	6.3	16.2
3. Columbia	135	0.6	13.7	8.1	21.8
4. Pacific-Coastal	507	2.4	65.5	20.8	86.3
5. Yukon	17	0.1	2.1	0.7	2.8
6. Mackenzie	31	0.1	2.9	2.1	5.0
7. Peace-Athabasca	209	1.0	18.5	14.3	32.8
8. Arctic-Coastal	11	0.1	0.4	1.2	1.6
9. Keewatin	4	0.1	-	0.5	0.9
10. Churchill	59	0.3	2.4	5.9	8.3
11. Nelson	219	1.0	11.1	20.6	31.7
12. North Saskatchewan	837	3.9	114.6	30.0	144.6
13. South Saskatchewan	948	4.4	137.0	29.2	166.2
14. Red-Assiniboine	1 282	5.9	173.1	47.6	220.7
15. Milk	15	0.1	-	1.9	1.9
16. Winnipeg	87	0.4	8.8	5.3	14.1
17. Northern Ontario	144	0.7	17.9	6.3	24.2
18. Northern Quebec	83	0.4	9.9	4.0	13.9
19. Upper Great Lakes	946	4.4	117.4	42.1	159.5
20. Southern Ontario	5 774	26.7	955.3	96.9	1 052.2
21. Ottawa	1 250	5.8	168.8	46.4	215.2
22. Mid-St. Lawrence	4 800	22.2	782.8	88.1	870.9
23. Quebec-Coastal	513	2.4	64.9	21.9	86.8
24. Saint John-St. Croix	369	1.7	38.6	21.2	59.8
25. Maritime Coastal	1 346	6.2	132.1	83.2	215.3
26. Newfoundland	522	2.4	57.0	28.5	85.5
Total	21 604	100.0	3 126.2	662.7	3 789.3

[1]Source: National Water Needs Study, Phase 1. Unpublished Draft Report, July 1972.

These data are from Leah (1977). Units have been converted from tons to tonnes.

TABLE 15

Potential Annual Releases of Plasticizer and Dissociation Products from Incineration in Selected Canadian Cities (tonnes)[1]

City	Tonnes	Drainage Basin
Charlottetown	2.3	Maritime Coastal
Dartmouth	2.3	Maritime Coastal
Halifax	8.2	Maritime Coastal
Alma, Quebec	0.9	Quebec Coastal
Quebec City	18.1	Mid-St. Lawrence
Montreal	45.4	Mid-St. Lawrence
St. Eustache, Quebec	1.4	Lower St. Lawrence
Algonquin Park	0.2	Ottawa
Hamilton	4.5	Southern Ontario
Toronto	36.3	Southern Ontario
Simcoe, Ontario	0.9	Southern Ontario
Dresden, Ontario	0.4	Southern Ontario
Port Colborne	0.9	Southern Ontario
Corunna	0.5	Southern Ontario
Collingwood	0.5	Upper Great Lakes
Regina	4.5	Milk River
Winnipeg	9.1	Red-Assiniboine
Powell River	0.5	Pacific Coastal
North Cowichan	0.2	Pacific Coastal
Total	137.1	

[1]Based on incineration tonnage and location data. Air Pollution Control Directorate, Ottawa, weighted by available demographic data.

These data are from Leah (1977). Units have been converted from tons to tonnes.

5. Accidental Spillage and Emergency Measures

According to Pazinski (1973) it does not appear that there will be any substantial input or entry of phthalate esters into the environment from man-made occurrences which would result in any large accumulation in one particular area which might be a cause of concern.

C. ENVIRONMENTAL INVOLVEMENT

1. Cycling and Fate of Phthalate Esters in the Environment

Autian (1973) discussed the transport of phthalate esters within the environment, as follows:

> "Since phthalate esters are being reported in different locations in the world and, in particular, in water bodies far removed from industrial centers, the question of how the phthalates reach these sites keeps arising. Information is now becoming available to indicate that trash no longer is confined to populated regions but that solid wastes are being seen thousands of miles from land. This past year there was a report that various types of plastic items have been found in ocean waters, indicating that these are becoming man-made pollutants far removed from the source of manufacture and use (Carpenter and Smith, 1972). Since a number of these plastic items may contain phthalate esters as plasticizers, it is possible that these esters are being released to the ocean and, in turn, are being ingested by various types of marine organisms, including fish.
>
> A more probable mechanism of transport of phthalate esters from sources of manufacture and use to remote sections of the country and world is through complexation with natural organic substances. For example, the esters may interact with fulvic acid which is present in humic substances in soils and waters. Since the fulvic acid-phthalate ester complex is soluble in water, the relatively insoluble esters can readily be carried off in water to other sections of streams, lakes, and oceans. Ogner and Schnitzer (1970) have, in fact, found four phthalate esters (di-2-ethylhexyl, dibutyl, dicyclohexyl, and benzyl butyl phthalate) in humic

substances as complexes with fulvic acid. These authors were extremely careful to preclude the possibility that these esters were contaminates and took very stringent steps in their processing to prevent contamination. Even though they leaned on the theory that the phthalate esters were most likely due to pollution, they did not completely rule out the fact that one or more of these same esters may have been biosynthetically produced in the humic material. It is clear, however, from their study that, if phthalate esters are discharged in one or more ways to soil and water, they can combine with fulvic acid and thus be transported away from the original site of pollution."

Matsuda and Schnitzer (1971) verified the fact that fulvic acid forms complexes with hydrophobic dialkyl phthalates, making the phthalates soluble in water. The extent of reaction was found to depend on the type of phthalate. Thus, one number-average molecular weight of fulvic acid dissolved four moles of bis (2-ethylhexyl) phthalate but only one mole of dibutyl phthalate, while two number-average molecular weights of fulvic acid interacted with three moles of dicyclohexyl phthalate. Infrared spectroscopy failed to produce evidence of the occurrence of chemical reactions between fulvic acid and the phthalates. The latter appeared to be absorbed on the surface of the fulvic acid molecule.

Corcoran (1973) reported that he found about 0.6 ppm of phthalates, assumed to be entirely di-(2-ethylhexyl) phthalate, in a sample of surface water from the Gulf of Mexico near South Pass off the Mississippi River. With the assumption that the effluent of the Mississippi River contained one-third of this concentration, he estimated that about 159×10^3 tonnes of DEHP would enter the Gulf of Mexico annually. Peakall (1975) has suggested that the result of Corcoran (0.6 ppm) must have been due to an abnormal local concentration or to an error in the analytical procedure, since in 1970 the total U.S. production of DEHP was also about 159×10^3 tonnes, representing about 40 percent of the total U.S. production of phthalates in that year.

Chan (1976) estimated that: (i) the rate of accumulation of DEHP in the Gulf of Mexico was about 230 tonnes per year and that of DBP was 91 tonnes per year; (ii) the rates of input of phthalates by ocean-dumping were about 27 tonnes of DEHP per year and 0.91 tonnes of DBP per year; (iii) the rates of

input through estuaries were about 45 tonnes of DEHP per year and 9.1 tonnes of DBP per year; and (iv) the rates of atmospheric input were greater than 140 tonnes of DEHP per year and 91 tonnes of DBP per year.

Dibutyl phthalate has been found in rainwater in Yokahama, Japan, at concentrations in the range from 1 to 250 ppb (Mori, 1976).

Phthalate esters may undergo biodegradation. This subject is discussed in Section 3.

The movement of phthalates in the environment has been reviewed by Peakall (1975).

Metcalf (1974) has described a standardized laboratory model ecosystem in which he used radiotracer methodology to evaluate the behaviour of various micropollutants, including phthalate esters. Each compound was studied for ecological effects over a terrestrial-aquatic interface and through several food chains, mainly to obtain quantitative information on ecological magnification and biodegradability.

The basic unit was a glass aquarium 25 cm x 30 cm x 46 cm with a polymethyl methacrylate top. To retard evaporation a screen wire portion was incorporated. A sloping shelf of 15 kg of washed white sand was bisected by a "lake" of seven litres of standard reference water. Sorghum vulgare plants were grown on the terrestrial shelf. A radio-labelled compound to be examined was usually applied to the leaves of the Sorghum. Marsh caterpillar larvae were added to consume the treated leaves and to serve as the dispersing agent for the radio-labelled compound. The lake contained a complement of microorganisms, plankton, Daphnia magna, Physa snails, and a clump of alga Oedogonium cardiacum. Culex fatigans mosquito larvae and Gambusia affinis fish were added later.

The results which Metcalf (1974) obtained for the distribution of radioactivity from di-(2-ethylhexyl) phthalate (DEHP) are shown in Table 16. On the basis of these results the author regarded DEHP to be a fairly stable environmental pollutant which is stored intact in the tissues of organisms. Considerable biomagnification was shown by high ecological magnification (E.M.) factors for the mosquito, the alga, and the snail. The fish was more successful in degrading DEHP to monoethylhexyl phthalate (MEHP), phthalic acid, and other products.

TABLE 16

Behaviour of Di-2-ethylhexyl Phthalate (DEHP) in the Model Ecosystem

	Concentrations (ppm, Equivalent) in				
	Water	Alga	Snail	Mosquito	Fish
Total ^{14}C	0.0078	19.105	20.325	36.609	0.206
DEHP	0.00034	18.322	7.302	36.609	0.044
MEHP	0.00099	0.325	2.541	--	0.021
Phthalic anhydride	0.00363	0.180	5.772	--	0.113
Phthalic acid	0.00077	0.094	2.724	--	0.018
Unknowns	0.00190	0.029	0.768	--	--
Polar metabolites	0.00016	0.155	1.218	--	0.010
E.M. values		E.M. = 53 890	21 480	107 670	130

These data are from Metcalf (1974).

2. Bioaccumulation

Bioaccumulation, which may also be called bioconcentration, and ecological or biological magnification, has been reported for phthalates in various species. Sanders et al. (1973) found that phthalate accumulation was rapid, resulting in body residues from 70 to 13 600 times the concentration of phthalates in the water, as is shown in Table 17 and 18. Metcalf (1974) reported ecological magnification (E.M.) values of 107 670 in the mosquito, 53 890 in the alga, 21 480 in the snail, and 130 in the Gambusia affinis fish, as is shown in Table 16, Section 1. Kadoma and Takai (1974c) found that the phthalate concentration factors of fish muscle were between 5×10^2 and 5×10^3 when the average phthalate concentration in the natural water was 0.1 ppb. They stated that the viscera contained from 3 to 5-fold the phthalate concentration of the muscle.

TABLE 17

"Biologic Magnification" of ^{14}C-Labelled Di-n-butyl Phthalate from Water by Six Species of Aquatic Invertebrates at 21°C

Organism	No. Per Sample	Water Concentration (µg/L ± SE[a])	Magnification Factor[b] After (days)			
			1	3	7	14
Midge larvae Chironomus plumosus	18	0.18 ± 0.015	3500	3000	6600	--
Waterflea Daphnia magna	180	0.08 ± 0.005	2200	3500	5000	5000
Scud Gammarus pseudolimnaeus	18	0.10 ± 0.010	1700	3700	6500	6700
Mayfly Hexagenia bilineata	9	0.08 ± 0.001	500	980	1900	--
Glass shrimp Palaemonetes kadiakensis	9	0.08 ± 0.001	1500	5000	--	--
Damselfly Ischnura verticalis	9	0.10 ± 0.005	1000	1600	2700	--

[a]Samples taken in triplicate and expressed as mean value ± SE (P = 0.05).

[b]The extracted radioactivity was assumed to be all ^{14}C-labelled di-n-butyl phthalate and the concentrations were derived from the original specific activity (1.64 mCi/mmole).

These data are from Sanders et al. (1973).

TABLE 18

"Biologic Magnification" of ^{14}C-Labelled Di-ethylhexyl Phthalate from Water by Five Species of Aquatic Invertebrates

Organism	No. Per Sample	Water Concentration (µg/L ± SE[a])	Magnification Factor[b] After (days)				
			1	3	7	14	21
Scud *Gammarus pseudolimnaeus*	18	0.1 ± 0.01	2800	5300	13600	13400	--
	18	62.8 ± 3.31[c]	30	100	116	279	260
Midge larvae *Chironomus plumosus*	18	0.3 ± 0.04	2400	2600	3100	--	--
Waterflea *Daphnia magna*	180	0.3 ± 0.04	1200	2500	5200	--	--
Mayfly *Hezagenia bilineata*	9	0.1 ± 0.01	850	1000	2300	--	--
Sowbug *Asellus brevicaudus*	4	1.9 ± 0.12[c]	--	--	80	71	70
	4	62.3 ± 3.31[c]	--	--	20	230	250

[a]Samples taken in triplicate and expressed as mean value ± SE (P = 0.05).

[b]The extracted radioactivity was assumed to be all ^{14}C-labelled di-ethylhexyl phthalate and the concentrations were derived from the original specific activity (1.64 mCi/mmole).

[c]Temperature = 25°C.

These data are from Sanders *et al.* (1973).

3. Pollution Reduction Measures

Biodegradation appears to be the best method for reducing pollution by phthalate esters.

Graham (1973) reported the results of laboratory biodegradability of di-(2-ethylhexyl) phthalate (DEHP) and butyl benzyl phthalate using a semicontinuous activated sludge at the feeding rate of 5 mg/48 hr. Within 48 hours 91 percent of DEHP and 99 percent of butyl benzyl phthalate disappeared, leaving no refractory residues.

Saeger and Tucker (1973a, 1973b) obtained primary and ultimate biodegradation data for several representative phthalate esters by using the Semi-Continuous Activated Sludge (SCAS) test of the Soap and Detergent Association (1965, 1969) and the River Die Away (RDA) test (Weaver and Coughlin, 1964). The SCAS test simulates what is probably the most widely used waste water treatment process and the RDA test closely represents a natural environmental situation. Results of the SCAS test, which are shown in Table 19 clearly demonstrate that phthalate esters readily undergo primary bacterial degradation. Reasonably rapid biodegradation of phthalates is also evident from the results of the RDA test, which are shown in Table 20.

Kodama and Takai (1975a, 1975b) found that dibutyl phthalate at the concentration of 3.6 kg/tonne in wastewater from phthalate ester manufacturing could be reduced to 0.36 kg/tonne (or 0.1 of the original concentration) by activated sludge treatment.

Johnson and Lulves (1975) reported the biodegradation of di-n-butyl phthalate (DBP) and di-(2-ethylhexyl) phthalate (DEHP) in freshwater hydrosoil. Samples of the esters, ^{14}C (carbonyl) labelled, were incubated aerobically and anaerobically for 1, 5, 7, 14 and 30 days. Under aerobiosis, 53 percent of the radio-labelled DBP was degraded within 24 hours and 98 percent within five days. In contrast, DEHP was only 50 percent degraded after 14 days. Under anaerobiosis, degradation of both esters was retarded. Using hydrosoil in a nitrogen atmosphere, DBP was degraded only one-sixth as fast and degradation of DEHP was not detected. Evidence from both thin-layer chromatography and radiorespirometry suggested that the esters underwent decarboxylation after initial hydrolysis, probably to 1, 2-dihydroxybenzene.

TABLE 19

Primary Bacterial Degradation

Semi-continuous Activated Sludge Test

Compound Tested	Addition Rate (mg/24 hrs)	% Degradation Rate ± 95% C.L.	Die-Away Half Life (Days)
1-Phenyl dodecane-p-sulfonate Sodium salt (LAS)	20	99+	< 0.1
Phthalic acid	50	99+	< 0.1
	100	99+	
	200	99+	
Butylphthalyl-butyl glycolate	5	99+	< 0.1
	20	99+	
	100	99+	
	200	99+	
Butylbenzyl phthalate	5	93±6	0.3
Di(2-ethylhexyl) Phthalate	5	70±11	0.8
	5	78±3	
Di(heptyl-undecyl) phthalate	5	52±10	1.5
	10	48±8	
	20	54±7	
Diundecyl phthalate	5	45±11	2.7
	20	29±7	

These data are from Saeger and Tucker (1973a).

TABLE 20

Primary Bacterial Degradation
River Die-away Test

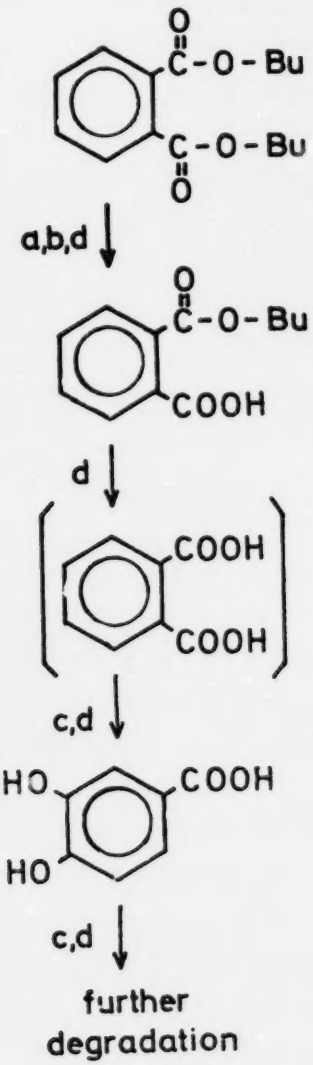
Compound Tested	Concentration (ppm)	Time for 50% Degradation (Weeks)
1-Phenyl dodecane -p-sulfonate Sodium salt (LAS)	3.2	0.8
Phthalic acid	12.5	1.5
Butylphthalyl-butyl glycolate	1.0	0.2
Butylbenzyl phthalate	1.0	0.2
Di(2-ethylhexyl) Phthalate	1.0	2.5
Di(heptyl-undecyl) phthalate	1.0	3.0
Diundecyl phthalate	1.0	2.5

These data are from Saeger and Tucker (1973a).

Several different soil microorganisms were tested by Engelhardt et al. (1975) for their ability to degrade the following phthalate esters: di-n-butyl, di-iso-butyl, di-n-octyl, di-(2-ethylhexyl), and dimethyl. All of these esters except dimethyl phthalate supported growth of the organisms. Dimethyl phthalate served as a carbon source for only two coryneform bacteria. Degradation products of the dialkyl phthalates were the corresponding monoesters. The overall reaction steps of di-n-butyl phthalate degradation by different soil microorganisms are depicted in Figure 6.

FIGURE 6

Degradation of Di-n-butyl Phthalate, Mono-n-butyl Phthalate and Phthalic Acid by Different Microorganisms: (a) Organisms Isolated With DBP as Carbon Source for Enrichment, (b) Stock Cultures, (c) and (d) Bacteria Isolated From Phthalic Acid Enrichment Medium



From Engelhardt et al. (1975).

Several additional, as yet unidentified metabolites with an intact phthalic acid moiety could be isolated from cultures of Penicillium lilacinum growing on di-n-butyl phthalate, di-n-octyl phthalate and di-(2-ethylhexyl) phthalate. This would indicate the existence of different metabolic pathways.

Mathur and Rouatt (1975) isolated a bacterium, tentatively identified as the saprophyte Serratia marcescens Bizio, that was found capable of growth on both di-(2-ethylhexyl) phthalate (DEHP) and di-n-octyl phthalate (DOP) at substrate concentrations up to 2.5 percent and on phthalic acid at concentrations below 1.25 percent. Phthalic acid seemed to be a primary product of the metabolism of DEHP and DOP.

Early in 1976, Saeger and Tucker (1976) reviewed various studies of biodegradation of phthalate esters and reported their own results for the biodegradability of phthalic acid, monobutyl phthalate, and five structurally diverse commercial grade phthalate ester plasticizers by naturally occurring, mixed microbial populations in river water and activiated sludge samples. The five Monsanto plasticizers studied were: butylglycolyl butyl phthalate (Santicizer B-16, lot QD-608), butyl benzyl phthalate (Santicizer 160, lot QA-1510), di-(2-ethylhexyl) phthalate (lot QL-1000), di-(heptyl, nonyl, undecyl) phthalate (Santicizer 711, lot QA-7911), and di-undecyl phthalate (lot EL-9139) . The compounds studied underwent rapid primary biodegradation in both unacclimated river water and acclimated activated sludge. When activated sludge acclimated to phthalic acid esters was used as the inoculum for the carbon dioxide evolution procedure, more than 85 percent of the total theoretical amount of carbon dioxide was evolved. According to Saeger and Tucker (1976) these studies demonstrated that the phthalate esters and intermediate degradation products readily undergo ultimate degradation in different mixed microbial systems at concentrations ranging from one to 83 mg/L.

Keyser et al. (1976) also reviewed recent studies of the biodegradation of phthalate esters and provided ample evidence, including some of their own data, to demonstrate that phthalate esters are biodegradable and that complete oxidative degradation of the aromatic ring usually occurs.

Varma et al. (1976) used wastewater organisms to metabolize diethyl phthalate (DEP). The results showed that variations in the number of resistant colonies on two sets of DEP medium plates were drastically different. Therefore the hypothesis of inducible enzyme formation in the acclimation process for biochemical oxygen demand (BOD) was rejected. The hypothesis that the metabolism originated through mutation was favoured by the authors.

Nagata et al. (1976) studied the microbial degradation of di-octyl phthalate (DOP) and di-butyl phthalate (DBP). The bacterial strain PB73 was used as a DBP-utilizing bacterium and the strain P032 as a DOP-utilizing bacterium. In media containing less than 20 percent of either ester, strain PB73 degraded 90 percent of DBP and strain P032 degraded 80 percent of DOP. The optimal growth of strain P032 was obtained at pH 7.4 at 34°C; that of strain PB73 was similar. Strain PB73 could degrade di-ethyl phthalate (DEP), di-butyl phthalate (DBP), and butyl phthalyl butyl glycolate (BPBG), but not di-octyl phthalate (DOP). Strain P032 could degrade DEP, DBP, DOP, and BPBG. Neither strain could degrade di-methyl phthalate (or terephthalic acid and its esters).

Engelhardt et al. (1977) have described the formation of metabolites by cultures of Penicillium lilacinum growing on different dialkyl phthalates. They identified the metabolites formed from di-iso-butyl phthalate. Di-n-butyl phthalate and di-iso-butyl phthalate were completely removed from the medium within a 30-day incubation period. From di-n-butyl phthalate two metabolites were isolated. The main product was shown to be the corresponding monoester; the second (minor) metabolite was not investigated further because of the small quantity produced. Di-iso-butyl phthalate gave one intermediate product, which was identified as 2-hydroxy-iso-butyl-iso-butyl phthalate and three products identified as mono-iso-butyl phthalate, di-(2-hydroxy-iso-butyl) phthalate and mono-2-hydroxy-iso-butyl phthalate. Only approximately one-half of the initial amount of either di-(2-ethylhexyl) phthalate (DEHP) or di-n-octyl phthalate was decomposed within 30 days. From DEHP the corresponding monoester, a second metabolite (which is hydroxylated in the alcohol moiety), and at least four minor metabolites were formed. Di-n-octyl phthalate was converted to seven metabolites, which were probably formed by ω- and (ω-1) - oxidation.

Some other pollution reduction measures have been reported, as follows:

Morita et al. (1973a) found that an average concentration of 4.3 ppb of dibutyl phthalate plus DOP, which presumably was di-(2-ethylhexyl) phthalate rather than di-n-octyl phthalate, in the Tama River in Japan could be effectively removed by coagulation with $Al_2(SO_4)_3$.

Mori (1976) reported that 2 ppm of activated carbon removed more than 90 percent of 0.5 ppb of dibutyl phthalate from water in 30 minutes. More than 50 ppm of activated carbon were needed to remove more than 90 percent of 1 ppm of dibutyl phthalate. Alum and chlorine were found to be less effective.

Porous polyurethane foam has been used successfully by Gough and Gesser (1975) to remove some phthalates at the parts per million level from water.

D. OCCURRENCE, RESIDUES AND CONTAMINATION

It is likely that some of the quantities of phthalate esters reported by various authors are erroneously high, probably because of contamination during sample preparation and from reagents (as has been described on page 22).

1. In Water, Air, Soil, and Food

(a) Water

Phthalate esters have not been monitored on a regular basis by government agencies in Canada. In 1975, the Ontario Ministry of the Environment conducted a survey of organic compounds in drinking waters (Smillie et al., 1977). As part of this survey 80 samples (of raw and finished drinking water from 29 water treatment plants) were analysed for five distinct phthalate esters, using gas chromatography (Meresz, 1977a). Of these samples, 39 were found to contain traces of phthalates. Twenty-two samples contained total phthalate concentrations between 0.05 and 1.0 µg/L, twelve samples contained between 1.0 and 3.0 µg/L, three samples contained between 3.0 and 5.0 µg/L, and two samples contained between 5.0 and 9.0 µg/L. Since these results were not confirmed by mass spectrometry they were not included in the report of Smillie et al. (1977). Also as part of this survey, ground water from Guelph, Ontario was analysed for phthalate esters. A concentration of 4.4 µg/L was found in one sample (Meresz, 1977b).

After making a ten-city survey of organic compounds in drinking water, the U.S. Environmental Protection Agency reported dibutyl phthalate concentrations which ranged from 0.01 to 5 µg/L, diethyl phthalate concentrations from 0.01 to 1 µg/L, and di-(2-ethylhexyl) phthalate concentrations from 0.4 to 30 µg/L. Dihexyl phthalate (0.16 µg/L), di-isobutyl phthalate (0.59 µg/L), and dimethyl phthalate (0.82 µg/L) were found in other studies (Anon., 1975a). In several cases, the phthalate levels in finished water were higher than those in raw water. The likely sources of phthalate contamination were plastic tubing and chemical storage containers used in water treatment plants. It is also possible that the occasionally higher measured levels of PAEs in finished water resulted from PAEs being trapped in the filter media and subsequently released. This phenomenon has been duplicated in laboratory studies carried out by the Ontario Ministry of the Environment. (Smillie et al., 1977).

Phthalates have also been found in drinking water supplies in Japan. Morita et al. (1973a) reported an average value of 4.3 ppb of dibutyl phthalate plus DOP, which presumably was di-(ethylhexyl) phthalate rather than di-n-octyl phthalate, in the Tama River, which provides the water supply of Tokyo. More recently, Morita et al. (1974) analysed many water samples from the Tama River. They found phthalate concentrations which ranged from 0.38 to 5.61 µg/L for di-n-butyl phthalate (DBP) and from 0.5 to 6.8 µg/L for di-(2-ethylhexyl) phthalate (DEHP). They also measured phthalate ester concentrations of Tokyo water. The raw water at the intake of filtration beds contained DBP at concentrations from 2.74 to 8.16 µg/L (mean value 4.5 µg/L) and DEHP at concentrations from 1.7 to 4.7 µg/L (mean value 2.7 µg/L). Cleaned water after coagulation contained lower mean concentrations of DBP (3.50 µg/L) and DEHP (1.8 µg/L). Tap water in Tokyo contained still lower mean concentrations of DBP (2.34 µg/L) and DEHP (1.6 µg/L). Neither DBP nor DEHP was detected in water from five shallow wells in metropolitan Tokyo.

Horibe et al. (1974) found DBP and DEHP in raw and finished water from eight Japanese water treatment plants. They reported that the concentrations of both phthalate esters increased after water treatment in most of the waterworks.

Kodama et al. (1975) found that the average concentration of DBP in rivers (in Aichi Prefecture) was 0.8 ppb. They stated that DEHP concentrations were generally lower. According to Takahashi et al. (1976) the highest concentration of phthalates found in streams (in Miyashiro Prefecture) was 7.6 ppb. The concentration of di-(2 ethylhexyl) phthalate was said to be higher than that of butyl phthalate.

Mori (1976) reported that dibutyl phthalate was the major ester found in the rainwater of Yokahama, Japan, at concentrations in the range from 1 to 250 ppb.

Recently, Tomita et al. (1977) have described some results taken from a report on environmental contaminants by the Japanese Agency of Environment (Anon., 1975b). Di-(2-ethylhexyl) phthalate was found in 176 (or 47 percent) of 375 samples of river water at concentrations ranging from not detectable to 0.015 ppm (mean value 0.00068 ppm) and di-n-butyl phthalate was found in 206 (or 55 percent) of these river water samples at concentrations ranging from not detectable to 0.036 ppm (mean value 0.00098 ppm).

Phthalate esters have been found in water samples other than drinking water. Mayer et al. (1972) analysed water samples from Lake Superior and Lake Huron for di-n-butyl phthalate (DBP) and di-(2-ethylhexyl) phthalate (DEHP). In water from Black Bay of Lake Superior (a rural and industrial area in Ontario) they found no detectable DBP but 300 ng/g (ppb) of DEHP. Water from Lake Huron contained 5.0 ng/g of DEHP but no detectable DBP. Water from Hammond Bay of Lake Huron, however, contained 0.04 ng/g of DBP but no detectable DEHP.

Phthalate esters in Lake Huron have also been measured as part of the Upper Lakes Reference Group study for the International Joint Commission. Four samples from Saginaw Bay of Lake Huron contained DEHP concentrations which ranged from less than 1 to 1.4 ug/L. The mean concentration was 1.3 µg/L (Anon., 1977).

Schacht (1974) reported phthalate concentrations found in the Illinois waters of Lake Michigan. Offshore water showed consistently low concentrations. In 1972, di-n-butyl phthalate was found in tributary streams in concentrations that ranged from a trace to 147.0 ppt; in 1971, it was not detected. Di-(2-ethylhexyl) phthalate was not detected in the tributary steams.

Hites (1973) reported phthalate concentrations from 0.88 to 1.9 ppb for several samples taken from the Charles River, near Boston, Mass.

In 1976, Giam et al. (1976b) reported mean concentrations of 14 ng of DBP per litre and 63 ng of DEHP per litre in the lower Mississippi River water as well as mean concentrations of 87.0 ng of DBP per litre and 112.0 ng of DEHP per litre in water samples from the northwestern part of the Gulf of Mexico. More recently, Giam et al. (1978) reported the phthalate concentrations shown in Table 21, some of which are for surface water.

(b) Sediments

Sediments in the Black Bay region of Lake Superior in Ontario have been found to contain dibutyl phthalate (100 ng/g or ppb) and di-(2-ethylhexyl) phthalate (200 ng/g or ppb) (Mayer et al., 1972).

Schacht (1974) reported high phthalate concentrations in some sediments of Lake Michigan tributaries in Illinois - di-n-butyl phthalate at a concentration of 120 ppb in Barat ravine (Lake Forest) and di-(2-ethylhexyl) phthalate at a concentration of 210 ppb in an unamed channel near Waukegan.

Dibutyl phthalate concentrations ranging from 200 to 290 µg/kg (ppb) have been measured in sediments of Saginaw Bay of Lake Huron. Sediments at Munising Harbor in Michigan contained phthalate concentrations up to 4.1 mg/kg (ppm) (Anon., 1977).

Phthalate esters at a concentration of 60 ppm have been found in the sediment of the Usk River in the United Kingdom (Eglinton, et al., (1975). Kodama et al. (1975) found dibutyl phthalate at a concentration of 0.24 ppb in the mud of Ise and Atsumi Bay in Aichi Prefecture, Japan. Giam et al. (1976b) reported mean concentrations of dibutyl

phthalate (3.0 ng/g or ppb) and of di-(2-ethylhexyl) phthalate (9.0 ng/g or ppb) in sediments of the Gulf of Mexico. More recent results of Giam et al. (1978) are shown in Table 21 .

TABLE 21

Mean Concentrations and Concentration Ranges of Two Phthalate Plasticizers in the Gulf of Mexico (39°00'N, 70°40'W) and the northern Atlantic (38°35'W); nd, none detected

Sample	Number of Samples	DBP		DEHP	
		Mean	Range	Mean	Range
			Surface water (nanograms per liter)		
Typical blank		<0.1		<0.2	
Mississippi delta	14	95	6.5-471	70	23-225
Gulf coast	10	74	3.4-265	130	6.316
Open gulf	7	93	3-133	80	6-97
North Atlantic +	10	nd	nd	4.9	0.1-6.3
			Sediment (nanograms per gram)		
Typical blank		<0.1		<0.2	
Mississippi delta	22	13	0.1-52.1	69	<0.1-248
Gulf coast	9	7.6	0.1-15.3	6.6	3.4-14.2
Open gulf	3	3.4	1.6-5.6	2.0	
			Air (nanograms per cubic meter)		
Typical blank		<0.03		<0.4	
Gulf of Mexico	8	0.3	0.08-0.7	0.4	<0.4-2.3
North Atlantic	5	1.0	0.4-2.3	2.9	1.4-4.1
			Biota (nanograms per gram)		
Typical blank		<0.1		<0.2	
Gulf of Mexico ≠	20	<0.1		4.5	< 1-135

+Part of a large intercalibration study (13).

≠Biota examined included, fish, crabs, shrimp, eel, rays, a jellyfish, and a starfish.

These data are from Giam et al. (1978).

Tomita et al. (1977) have described some results taken from a report on environmental contaminants by the Japanese Agency of Environment (anon., 1975b). Di-(2-ethylhexyl) phthalate was found in 224 (or 61 percent) of 370 samples of sediment at concentrations ranging from not detectable to 17 ppm (mean value 0.48 ppm) and di-n-butyl phthalate was found in 163 (or 44 percent) of these sediment samples at concentrations ranging from not detectable to 2.3 ppm (mean value 0.08 ppm).

(c) Air

There is very little available information on phthalate ester concentrations in ambient air.

Giam et al. (1976b) reported some preliminary atmospheric measurements of phthalates over the Gulf of Mexico. The mean concentrations in air were 0.3ng/m^3 for dibutyl phthalate and 0.4 ng/m^3 for di-(2-ethylhexyl) phthalate. More recent results of Giam et al. (1978) are shown in Table 21 (Section D.1.a.). Higher mean concentrations in air over the North Atlantic Ocean were 1.0 ng/m^3 for dibutyl phthalate and 2.9 ng/m^3 for di-(2-ethylehxyl) phthalate.

Several phthalates have been positively identified by Thomas (1973) in air samples collected near a municipal incinerator in Hamilton, Ontario. The concentrations of di-n-butyl phthalate, di-(2-ethylhexyl) phthalate, and butylphthalyl butyl glycolate found were 700, 300, and 750 ng/m3, respectively. Evidently these concentrations are much higher than one would expect in ambient air.

According to Shea (1971) the "new car smell" and the thin film of sticky material which often deposits on automobile windshields (fogging) are largely due to evaporation of phthalate esters and other plasticizers from the plastic interiors of cars. Mathur (1974) has stated that Graham (1973) had reported that the air in a new car was found to contain phthalic acid esters at the nanogram per litre (or µg/m^3) level, due to losses from the vinyl upholstery. Actually, Graham (1973) had reported that an analysis of the atmosphere inside a new automobile, which was driven approximately 2,000 miles during which no smoking, dining, or storage of materials was permitted, disclosed a concentration of 12 µgL (mg/m^3) of organic material composed of

more than 60 compounds. The phthalate portion of this mixture was found to range from 0 to 6 percent, depending upon temperature conditions. At the lower temperatures, the phthalates were undetectable. Some of the other organic materials found were: C_2 to C_{19} alkylbenzenes, C_9 to C_{18} alkanes, higher alkanes, naphthalene, phenol, and di-tert-butyl cresol.

Contamination of spacecraft by phthalate esters has been described by Gross and Colony (1973), who have noted that the very low vapour pressures of phthalates (5×10^{-8} mm Hg at temperatures from 52 to 84°C, 5×10^{-6} mm Hg at temperatures from 105 to 138°C, as shown in Table 1 in Section A.2) become very significant in spacecraft which experience pressures as low as 10^{-7} mm Hg in test and much lower pressures in flight for periods as long as several years at average temperatures of 25 to 40°C.

Men'shikova (1971) reported dibutyl phthalate concentrations from 0 to 1.22 mg/m^3 in the air of shipboard living quarters, even three years after the vessel examined was built. She thought is was probable that the dibutyl phthalate came from polyvinyl chloride (PVC) linoleum, decorative laminated plastics, and pavinols (leather substitutes).

In a study of an experimental mobile home, which had been made with the extensive use of plastics, Styazhkin et al. (1976) found concentrations in air as follows: phthalates, 3.8 mg/m^3; ammonia, 1.1 mg/m^3; formaldehyde, 0.3 mg/m^3; and phenol, 0.03 mg/m^3. The authors regarded the mobile home as unsuitable for human habitation.

(d) Soil

Ogner and Schnitzer (1970; Leah, 1977) studied a humus from Prince Edward Island and found phthalate-fulvic acid complexes with levels of 13 mg of phthalate per 100 g of fulvic acid, up to 0.03 percent (or 300 ppm) dry weight.

(e) Food

Morita et al. (1973b) analysed for dibutyl phthalate (DBP) and di-(2-ethylhexyl) phthalate (DEHP) in vegetables, fruits, fish, meat, milk, butter, and cheese. The phthalates were detected only in rainbow trout (0.6 ppm) and butter (4 to 11 ppm). The authors stated that the phthalates in butter orgininated in the wrappings.

Twenty-one samples of fish available to Canadian consumers have been analysed by Williams (1973) for DBP and DEHP. Only very low levels of these phthalate esters were detected in any of the fish. Dibutyl phthalate was found in individual canned samples of tuna (78 ppb) and salmon (37 ppb). Traces were also found in a second sample of canned salmon and in one of two other samples of canned tuna, as well as in three samples of unprocessed pickerel from Lake Ontario and in one sample of canned shrimp. Di-(2-ethylhexyl) phthalate was found in three samples of canned tuna (40, 140 and 160 ppb), two samples of canned salmon (63 and 89 ppb), and in one sample of unprocessed eel (104 ppb). Traces were also found in two of three samples of unprocessed pickerel from Lake Ontario, in a sample of unprocessed catfish from Lake St. Pierre, and in samples of processed frozen rainbow trout, ocean perch and mackerel. The most highly contaminated sample was one of canned tuna which contained DBP at 78 ppb and DEHP at 160 ppb to give a total phthalate concentration of 238 ppb. Neither of these phthalates was detected in samples of canned sardine, crab and baby clams, or in samples of processed frozen sole, oyster and scallop.

Phthalates have been found in Great Lakes fish, notably Lake Superior fish where levels were in the range of 5 to 10 mg/kg (ppm) and 18 to 20 mg/kg (ppm) in selected tissues (Anon., 1977).

Several Lake Michigan fish species have been found (Schacht 1974) to contain phthalates, as follows: DBP from not detectable to 0.1 ppm, DEHP from not detectable to 1.3 ppm.

Kodama and Takai (1974c) found that the phthalate concentrations in fish muscle ranged from 0.05 to 0.5 ppm. The viscera contained three-to five-fold the phthalate concentration of the muscle.

Sato et al. (1974) found dibutyl phthalate and di-(2-ethylhexyl) phthalate in salt and in sugar, at the concentrations shown in Table 22.

Kodama et al. (1975) found dibutyl phthalate ($\geq$0.4ppm) and di-(2-ethylhexyl) phthalate ($\geq$0.27 ppm) in ten samples of fish in Aichi Prefecture, Japan.

Tomita et al. (1977) have reproduced some 1975 results from a report (Anon., 1975b) of the Japanese Agency of Environment. In 332 samples of fish (actually shellfish) examined, di-n-butyl phthalate was found in 122 (or 37 percent) of the samples at concentrations which ranged from not detectable to 2.0 ppm (mean value 0.13 ppm) and di-(2-ethylhexyl) phthalate was found in 92 (or 28 percent) of the samples at concentrations which ranged from not detectable to 19 ppm (mean value 0.29 ppm).

TABLE 22

Phthalate Esters in Salt and Sugar

(Units ppm)

Sample	DBP[a)]	DEHP[a)]
Kitchen salt A	2.20	nd
Kitchen salt B	nd	nd
Kitchen salt C	0.80	nd
Kitchen salt D	0.09	nd
Kitchen salt E	0.52	nd
Kitchen salt F	1.27	nd
Table salt A	2.23	8.8
Table salt B	2.55	7.6
Table salt C	2.18	nd
Table salt D	0.52	nd
Refined salt A	0.90	0.06
Refined salt B	0.13	nd
Flake grade salt	0.075	nd
Solar salt	nd	nd
NaCl reagent (E.P.)	0.05	nd
White sugar A	1.25	0.08
White sugar B	0.025	nd
Granulated sugar A	0.50	0.06
Granulated sugar B	nd	nd
Granulated sugar C	nd	nd

a) experimental condition 4) in Table 1.

nd = not detected.

These data are from Sato et al. (1974).

Tomita et al. (1977) also analysed for di-n-butyl phthalate (DBP) and di-(2-ethylhexyl) phthalate (DEHP) in 22 kinds of commercial Japanese foods (55 samples, 17 of which were fatty foods and 38 of which were nonfatty foods). Total DBP and DEHP concentrations higher than 1.0 ppm were found in 4 fatty and 12 nonfatty foods. Instant vegetable cream soup in paper-aluminum plastic packages showed the highest values of DBP of 6.35 ppm among fatty foods, while a sample of tempura powder (for frying) showed 9.33 ppm of DBP and 16.26 ppm of DEHP, which were the highest values found by Tomita et al. (1977). A sample of corn starch contained 4.27 ppm of DEHP but DBP was not detected in this sample.

According to Leah (1977) packaging is a major source of PAEs in food. Phthalates may migrate from some flexible polyvinyl chloride (PVC) wraps into certain foods, particularly into foods with a high fat content such as meat and dairy products. Foils coated with plasticized nitrocellulose or vinyl chloride/vinyl acetate copolymer released DBP and DEHP into lard and cheese samples wrapped therein (Pfab, 1967). The migration of phthalic acid esters from packaging film to foodstuffs, as reported by Tomita et al. (1977), is shown in Table 23.

Hartung (1976) also discussed phthalates in foods. In the United States the Food and Drug Administration (FDA), Bureau of Foods (Anon., 1974a; Anon., 1975c) analysed a number of foods for PAE residues. In a survey of residues in fish (Anon., 1974a) most fish were found to contain only traces of DBP and DEHP of about 0.2 ppm (the detection limit). Samples containing more than 0.2 ppm of DEHP were found in Long Island Sound, San Francisco Bay, and Lake Michigan. The residues of DEHP rarely exceeded 1 ppm. Di-n-butyl phthalate was found mostly in fish from Lake Michigan (average 0.40 ppm) and the lower Mississippi River (average 0.38 ppm).

The follow-up study (Anon., 1975c) involved a wider sampling of foods, including: baked beans, cornmeal, canned corn, white bread, eggs, cereal, meat, margarine, processed American cheese, and milk. Margarine showed low contamination except for three samples which contained the highest levels of PAEs found (13.7 and 56.3 ppm, on a fat basis).

TABLE 23

Migration of Phthalic Acid Esters from Packaging Film to Foodstuffs[a]

		Time After Manufacture (Months)	Packaging materials (ppm)				Foodstuffs (ppm)		
			Materials[b]	DNBP	DEHP	Total	DNBP	DEHP	Total
Tempura (frying) powder	A	3	Pl-L	70.28	3675.0	3745.28	14.70	68.08	82.78
	B	4	Pl-L	6.29	2.30	8.59	0.39	0.11	0.50
Instant cream soup	A	14	P-Al-Pl	23.17	1.35	24.52	1.73	0.04	1.77
	B	?	P-Al-Pl	588.16	58.92	647.08	60.37	2.15	62.52
	C	?	P-Al-Pl	588.75	58.93	647.68	51.79	3.01	54.80
Instant soybean soup		?	P-Pl	2.75	1.85	4.60	nd[c]	nd	nd
Soft margarine		4	Pl	1.29	1.44	2.73	nd	nd	nd
Fried potato cake	A	1	Pl-L	10.86	385.85	396.91	1.11	0.05	1.16
	B	?	Pl-L	10.66	1.28	11.94	nd	nd	nd
	C	?	Pl-L	22.98	11.80	34.78	1.21	9.06	10.27
Orange juice		1	P-Pl	1.52	0.74	2.26	0.35	0.05	0.40
Red ginger pickles		?	Pl	3.00	2.14	5.14	0.11	nd	0.11
Sugar		?	Pl	7.24	2.75	9.99	nd	nd	nd
Table salt		?	P-Pl	5.18	2.58	7.76	nd	nd	nd

[a]The analyses were done during September and October 1975.

[b]Pl plastics: L, laminated film; P, paper; Al, aluminum foil.

[c]nd. Not detectable.

These data are from Tomita et al. (1977).

Bread, eggs, cereal, cornmeal, and meat were found to contain very low residues of PAEs. Milk and cheese showed extensive contamination by DEHP. Most cheese samples contained less than 5 ppm (fat basis) but the highest levels reported were 22.8 and 24.9 ppm of DBP (fat basis) and 35 ppm of DEHP (fat basis). Nearly all milk samples contained DEHP and the highest level found was 31.4 ppm (fat basis). It was mentioned in the report that there was a strong suspicion that there had been cross-contamination, especially involving the dairy product samples.

The occurrence of phthalate esters in edible plants has been mentioned in review articles by Mathur (1974) and by Peakall (1975).

2. In Terrestrial Animals and Plants

Dioctyl phthalate, which may actually have been di-(2-ethylhexyl) phthalate, has been found in the pineal glands of cattle (Taborsky, 1967; Peakall, 1975; and Hugos, 1972a).

Nazir et al. (1973; Marx, 1972) reported high concentrations of di-(2-ethylhexyl) phthalate (13.5 mg/100 g of muscle) in the lipid fractions of beef heart mitochondria. They also detected lower concentrations in the mitochondria of rabbit, rat, and dog heart muscle.

Jones et al. (1973; Peakall 1975) have reported the natural occurrence of 1.75 ppm of dibutyl phthalate in the cockroach.

Low levels of phthalate esters in various plants have been mentioned in review articles by Mathur (1974) and by Peakall (1975).

3. In Aquatic Organisms

Phthalate ester concentrations in fish and other types of seafood have been reported in Section D.1.e.

Giam et al. (1978) analysed various biota from the Gulf of Mexico for di-n-butyl phthalate and di-(2-ethylhexyl) phthalate. The biota examined included fish, crabs, shrimp, eel, rays, a jelly-fish, and a starfish. They reported (see Table 21, Section D.1.a) that DEHP concentrations ranged from less than 1 to 135 ng/g (ppb) with a mean value of 4.5 ng/g (ppb). The mean concentration of DBP was less than 0.1 ng/g (ppb).

4. In Human Tissue

Jaeger and Rubin (1972) reported that di-(2-ethylhexyl) phthalate was extracted from polyvinyl chloride (PVC) blood bags by both human and dog blood stored at 4°C at a rate of 0.25 ± 0.03 mg/100 ml-day. More recently, Jaeger and Rubin (1973b) have shown that several plasticizers, including di-(2-ethylhexyl) phthalate (DEHP) and butylglycolyl butyl phthalate (BGBP), may be extracted from PVC tubing by human and animal blood.

Valeri et al. (1973) reported the presence of significant amounts of di-(2-ethylhexyl) phthalate in human blood after storage in poly (vinyl chloride) plastic containers.

Maxwell et al. (1973) found no phthalates (even at the level of 0.025 mg percent) in the blood of 25 randomly selected normal individuals.

Vessman and Rietz (1974) found DEHP in human plasma stored in plastic bags. The DEHP concentrations ranged from 40 to 120 µg/ml (or from 0.6 to 1.7 mg/g of protein).

Mes et al. (1974) found di-n-butyl phthalate (DBP) and di-(2-ethylhexyl phthalate (DEHP) in human adipose tissue collected during autopsies on accident victims. In most samples the concentration of DBP was in the range from 0.10 to 0.30 ppm and the concentration of DEHP was in the range from 0.30 to 1.00 ppm.

Tomita et al. (1977) have reported concentrations of DBP and DEHP in human blood, before and after meals. Their results are shown in Tables 24 to 26.

TABLE 24

Levels of Phthalic Acid Esters in Human Blood Before Meals[a]

No.	Sex[b]	Age	DNBP (ppm)	DEHP (ppm)	Total (ppm)
1	m	31	0.04	0.02	0.06
2	f	21	0.06	nd[c]	0.06
3	m	40	0.01	0.01	0.02
4	m	22	0.01	0.01	0.02
5	f	21	0.01	0.01	0.02
6	f	22	0.01	0.01	0.01
7	f	30	0.01	0.01	0.02
8	m	23	nd	nd	nd
9	m	25	nd	nd	nd
Average			0.02	0.01	0.02

[a]The analyses were done in September 1974. All values are parts per million on a whole blood basis.

[b]m, male; f, female.

[c]nd. Not detectable.

These data are from Tomita et al. (1977).

TABLE 25

Levels of Phthalic Acid Esters and PCBs in Human Blood After Meals[a]

No.	Sex[b]	Age	DNBP (ppm)	DEHP (ppm)	Total (ppm)	PCBs (ppm)
1	m	21	0.17	0.18	0.35	
2	f	22	0.18	0.14	0.32	0.002
3	f	23	0.08	0.20	0.28	
4	m	30	0.16	0.11	0.27	0.004
5	f	22	0.07	0.17	0.24	
6	f	21	0.10	0.13	0.23	0.007
7	m	22	0.08	0.15	0.23	
8	f	22	0.09	0.11	0.20	
9	f	22	0.14	0.05	0.19	
10	f	22	0.05	0.13	0.18	0.020
11	f	21	0.03	0.13	0.16	0.008
12	m	29	0.05	0.10	0.15	0.005
13	f	21	0.05	0.08	0.13	0.004
Average			0.10	0.13	0.23	0.007

[a]The analyses were done from June 1973 to February 1974. All values are parts per million on a whole blood basis.

[b]m, male; f, female.

These data are from Tomita et al. (1977).

TABLE 26

Levels of Phthalic Acid Esters in Human Blood Before and After Meals[a]

No.	Age[b]	Before		After	
		DNBP	DEHP	DNBP	DEHP
1	31	0.06	0.07	0.11 (1.82)[c]	0.17 (2.43)
2	22	0.05	0.07	0.15 (3.00)	0.28 (4.00)
3	22	0.06	0.05	0.03 (0.50)	0.06 (1.20)

[a]The analyses were done in February 1975. All values are parts per million on a whole blood basis.

[b]All samples from males.

[c]Numbers in parentheses are increased ratios.

These data are from Tomita et al. (1977).

E. EXPERIMENTAL TOXICOLOGY

1. Metabolism

A summary of studies of the metabolism of phthalate esters is shown in Table 27. More complete details of these studies are given below.

Jaeger and Rubin (1973a) showed that an unknown compound, which was probably glycolyl phthalate, was a metabolite of butylglycolyl butyl phthalate (the plasticizer in the PVC tubing used) in an isolated, perfused rat liver system. Jaeger and Rubin (1973b) injected 40 mg of di-(2-ethylhexyl) phthalate (DEHP) intravenously into two rats. The rats were sacrificed 24 hours later and the distribution of DEHP in various tissues was determined. The results are shown in Table 28.

TABLE 27

Summary of Studies of the Metabolism of Phthalate Esters

Substrate	Route of Administration and Species	Organ Analysed or Main Target	Metabolites	Rates of Elimination of Metabolite or Substrate	Reference
butyl glycolyl butyl phthalate		isolated, perfused rat liver system	glycolyl phthalate (probably)		Jaeger and Rubin (1973a)
DEHP (40 mg)	rat	See Table 28			Jaeger and Rubin (1973b)
DEHP	(i.v.) rat		four chemically similar water-soluble metabolites		Schulz and Rubin (1973)
DEHP (1 ug/L)	catfish		MEHP, the corresponding monoester glucuronide (unknown aglycone), phthalic acid, and a phthalic acid glucuronide		Stalling et al. (1973)
DEHP (0.1% in fat free or normal diets)	rat	heart, epididymal fat pad			Stein et al. (1973)
DEHP	(oral) rat			rapid	Rubin (1973)
DEHP (i.v.)	(i.v.) rat	liver		$t_{\frac{1}{2}}$ 9 min.	
DEHP (2.9 mg/kg) in corn oil	rat			88% within 48 hours	
DEHP (1000 ppm) for 7 days, then 14C-DEHP	rat			95% within 4 days	Daniel (1973)
DEHP (5000 ppm)	(diet) rat	liver		$t_{\frac{1}{2}}$ 1 to 2 days	
		fat		$t_{\frac{1}{2}}$ 4 to 7 days	
DEHP (i.v.) emulsion in oleic acid (600 mg/kg)	rat	liver and lung	4 major and several minor	$t_{\frac{1}{2}}$ 1 to 2 days	
DEHP	rat		only those metabolites expected from ω- and (ω-1)-oxidation of MEHP, phthalic acid (<3%)		Albro et al. (1973)
dimethyl phthalate	rat		phthalic acid		

TABLE 27 (Cont'd)

Summary of Studies of the metabolism of phthalate esters

Substrate	Route of Administration and Species	Organ Analysed or Main Target	Metabolites	Rates of Elimination of Metabolite or Substrate	Reference
DBP, DOP	rat		diesters, triesters, ketodiesters, two classes of hydroxy-diesters, the corresponding monoesters, metabolites expected from ω- and (ω-1)-oxidation.		Albro and Moore (1974)
DEHP in the diet	rat	liver fat		$t_{\frac{1}{2}}$ 1 to 2 days $t_{\frac{1}{2}}$ 3 to 5 days	
DEHP	(i.v.) rat	liver, lung and spleen		$t_{\frac{1}{2}}$ 1 to 2 days	Daniel and Bratt (1974)
DEHP	(oral) rat		acid, alcohol and ketone resulting from ω- and (ω-1) oxidation of MEHP		
DEHP (large single dose)	rat		5 to 10 unknown metabolites in feces, 4% MEHP and 7 other metabolites in urine. Phthalic acid on hydrolysis of urine.		Williams and Blanchfield (1974)
DEHP (0.1% of diet)	rat		similar metabolites but no MEHP		Williams and Blanchfield (1974)
DBP	rat		phthalic acid, mono-butyl phthalate, mono-3-hydroxybutyl phthalate, mono-4-hydroxybutyl phthalate		Williams and Blanchfield (1975)
DEHP	(oral) rat		4 major metabolites in urine, unchanged DEHP in feces		Tanaka et al. (1975)
DEHP	intraperitoneal rat	blood, fetal tissue, amniotic fluid, placentas		$t_{\frac{1}{2}}$ 2.33 days	Singh et al. (1975)
diethyl phthalate	rat	blood, fetal tissue, amniotic fluid, placentas		$t_{\frac{1}{2}}$ 2.22 days	
MEHP	(oral) rat		an alcohol, a ketone and an acid resulting from side-chain oxidation of MEHP, trace of phthalic acid	80% of dose in 24 hours	Chu et al. (1978)

TABLE 28

Intravenous DEHP Rat Tissue Levels After 24 Hours

Tissue	Concentration, mg/g or mg/ml	DEPH Recovered from Tissue, mg	% of Injected Dose Recovered
Liver	1.6	21.82	27.3
Lung	8.18	21.26	26.6
Carcass	0.06	16.66	20.8
Spleen	1.89	2.65	3.3
Kidney	0.08	0.26	0.3
Heart	0.08	0.14	0.2
Gut	< 0.01	0.12	0.2
Blood	< 0.01	0.03	< 0.01
Brain	< 0.01	0.01	< 0.01
Testicle	< 0.01	0.01	< 0.01
Feces	< 0.01	0.334	0.4
		Total	79.1

These data are from Jaeger and Rubin (1973b).

Schulz and Rubin (1973) showed that in rats intravenous DEHP disappears rapidly from the bloodstream and is localized primarily in the liver. This occurred whether the DEHP was administered as a solution or as an emulsion. Varying amounts of DEHP were found in the lungs, ranging from less than two percent after 24 hours for finely emulsified preparations to more than 30 percent, with long-term retention, for poorly emulsified preparations. Thus, the clearance of DEHP by the pulmonary circulation was found to be highly dependent upon the dimensions of the oil droplets presented to it. On the other hand, clearance by the liver appeared to occur readily, regardless of the degree of emulsification. However, the hepatic uptake process appeared to be saturated at a DEHP dose of 200 mg/kg as was suggested by a slower rate of disappearance of this higher dose from the blood.

Di-(2-ethylhexyl) phthalate appeared to be extensively metabolized by the rat to water-soluble metabolites which were excreted primarily in the urine and feces. Thus, an intravenous dose of 0.1 mg of DEHP/kg of body weight could be almost totally accounted for as excreted water-soluble metabolites within 24 hours after administration.

Following oral administration of 200 mg/kg, the metabolism of DEHP and excretion of the metabolites were so rapid relative to the rate of absorption of DEHP from the gastrointestinal tract that no significant quantities of DEHP could be found in the blood or tissues. Finally, preliminary results of Schulz and Rubin (1973) showed that metabolism of DEHP by the rat does not consist of simple stepwise de-esterification of the dialkyl ester. Rather, at least four chemically similar water-soluble metabolites were found but not identified.

Stein et al. (1973) fed different diets to four groups of male, weanling, albino rats. One basic diet contained four percent fat; the other was fat-free. Two other diets were prepared by supplementing the two basic diets with 0.1 per cent of di-(ethylhexyl) phthalate (DEHP). Addition of DEHP to either fat-free or normal diets resulted in significant hypertrophy of the liver (after six weeks). It was also observed that addition of DEHP to these diets did not result in an accumulation of DEHP in the liver. In contrast, supplementation of the diets with DEHP resulted in a significant deposition of DEHP in the heart for both dietary groups. Di-(2-ethylhexyl) phthalate was also found to accumulate in the epididymal fat pad of animals fed DEHP. Dietary DEHP had a significant influence on the total weight of the epididymal fat pad in the following manner. Animals on the four percent fat diet showed an increase in fat pad weight, while those on the fat-free diet showed a decrease upon adidition of DEHP to the respective diets. In other words, addition of DEHP to these diets resulted in an equal but opposite effect on this tissue.

Stalling et al. (1973) reported that metabolism of phthalate esters in fish occurred in vivo and in vitro. Static exposures of catfish (2 g) to 1 µg/L of ^{14}C-labelled DEHP for 24 hours resulted in tissue residues of 2.6 µg/g. Four metabolic products were separated and identified. These were: mono-2-ethylhexyl phthalate (the predominant metabolite), the corresponding monoester glucuronide (unknown aglycone), phthalic acid, and a phthalic acid glucuronide.

Dibutyl phthalate (DBP) was metabolized in vitro sixteen times more rapidly than DEHP by hepatic microsomes from male channel catfish.

Rubin (1973) reported absorption, distribution, metabolism, and excretion studies of DEHP in rats. Absorption of DEHP after oral administration was found to be so slow relative to the rates of metabolism and excretion that only trace or no significant amounts of DEHP were found in blood or tissues and the total administered dose could be almost entirely accounted for as metabolic products excreted in the urine and feces. Following intravenous administration, DEHP disappeared rapidly from the blood (with a half-life of less than nine minutes) and accumulated in the liver (50 percent of the injected dose after one hour). During the subsequent 24 hours the DEHP disappeared from the liver and water-soluble metabolites were found in urine and feces.

Daniel (1973) reported the investigation of the kinetics of absorption, excretion and tissue distribution of DEHP (carbonyl - ^{14}C) in rats.

When male, Wistar rats were given a single oral dose of a solution of ^{14}C-DEHP (2.9 mg/kg), in corn oil, an average of 42 percent (range 36 to 50 percent) of the radioactivity was excreted in the urine and 57 percent, (range 50 to 69 per cent) in the feces in seven days. Most (88 percent) of the material was eliminated within 48 hours of dosing. In experiments with rats in which the bile duct was cannulated, 14 percent (range 12 to 15 percent) of the ^{14}C was recovered from the bile in 96 hours. When rats were fed a diet containing 1000 ppm of DEHP for seven days and then dosed with ^{14}C-DEHP, about 57 percent of the radioactivity was excreted in the urine and 38 percent in the feces within four days. This treatment did not significantly reduce the amount of ^{14}C excreted (9 percent) in the bile. These data demonstrated that while DEHP is incompletely absorbed from the intestine, the amount absorbed may increase following continuous ingestion of the ester.

The rate and extent of accumulation of DEHP, and those of any of its metabolites, were investigated in several tissues in rats that were maintained for 5 to 7 weeks on diets containing ^{14}C-DEHP.

At a dietary concentration of 1000 ppm, the amount of ^{14}C in abdominal fat increased steadily during the first two weeks of feeding to a concentration equivalent to 7 ppm of the ester. This value did not alter during the subsequent three weeks of continuous feeding of the experimental diet. A steady-state concentration of 45 ppm was achieved in the liver within four days. The

amount of radioactivity in the brain never exceeded 1 ppm, calculated as DEHP. The concentration in the heart was more variable (1 to 8 ppm). Analysis of the fat demonstrated that the radioactive material was DEHP.

Equilibrium concentrations were achieved at similar times in the tissues of rats fed 5000 ppm of DEHP in the diet, although at higher concentrations, namely 70 ppm for fat, 120 to 140 ppm for liver and 15 ppm for heart. When the remainder of the animals from both experiments were returned to a normal diet, the amount of ^{14}C in liver and fat declined with half-lives of 1 to 2 and 4 to 7 days, respectively.

These experiments demonstrated that no accumulation of DEHP, or of any of its metabolites, is likely to occur following the ingestion of foodstuffs containing residues of the ester.

The tissue distribution and excretion of radioactivity was also studied after the intravenous administration to rats of an emulsion (0.3 mL), average particle size, 0.5 μm, of DEHP in oleic acid (600 mg/kg). These experiments were designed to simulate absorption through the skin and the use of DEHP as a plasticizer in various biomedical preparations.

Within two hours of dosing, radioactivity was present in liver (38 percent), lung (26 percent) and fat (0.9 percent). The amount of ^{14}C in liver and lung declined steadily during the subsequent four days at which time 44 percent of the radioactivity had been excreted in the urine and an additional 29 percent in the feces. The half-life of the ester in liver and lung was estimated at between 1 and 2 days. Analysis of urine and bile showed the presence of four major and several minor radioactive components.

Albro et al. (1973) reported that the only metabolites found in the urine of rats fed ^{14}C-labelled DEHP were those to be expected from ω- and (ω-1)-oxidation of mono-2-ethylhexyl phthalate, without attack on the aromatic ring. Conjugates were apparently not formed, and free phthalic acid amounted to less than three per cent of the urinary metabolites.

Albro and Moore (1974) extended this study to rat urinary metabolites of dimethyl, di-n-butyl, and di-n-octyl phthalate. The types of metabolites isolated were said to be diesters, triesters, ketodiesters, and two classes of hydroxydiesters. Phthalic acid was a very minor metabolite except in the case of dimethyl phthalate precursor. The corresponding monoesters became more

significant as they became more polar (methyl>butyl>n-octyl≈ethylhexyl). The remaining metabolites were those that would be expected from (ω-1)-and ω-oxidation of the monoesters. Intact diester was excreted as a trace component when dibutyl phthalate was fed and as a significant component when dimethyl phthalate was fed.

Albro and Latimer (1974) have studied nonspecific lipase activity in extracts of rat pancreas, using phthalate esters as selective substrates.

Daniel and Bratt (1974) studied the absorption, metabolism and tissue distribution of di-(2-ethylhexyl) phthalate in rats. Rats given a single oral dose of ^{14}C-labelled DEHP excreted 42 percent of the dose in the urine and 57 percent of the dose in the feces in seven days. A significant proportion (14 percent) of the dose was excreted in bile and it was apparent that little, if any, of the material in bile was reabsorbed from the intestine. Rats feed 1000 ppm of DEHP in the diet for seven days before dosing with ^{14}C-labelled DEHP excreted 57 percent in the urine and 38 percent in the feces in four days.

When DEHP was fed continuously to rats at dietary concentrations of 1000 and 5000 ppm, the amounts of the ester in liver and abdominal fat rapidly attained steady-state concentrations and there was no evidence of accumulation. When returned to a normal diet, the radioactivity in the liver declined with a half-life of one to two days and the radioactivity in the fat declined with a half-life of 3 to 5 days. The liver weight relative to total body weight increased to a level of 50 percent above normal in rats receiving 5000 ppm of DEHP and returned to normal within one week after being returned to normal diet. When administered intravenously DEHP was preferentially localized in liver, lung and spleen from where it was eliminated with a half-life of 1 to 2 days.

The hexobarbital sleeping time was reduced by 30 to 40 percent in rats following repeated oral administration of DEHP; when the ester was administered intravenously the sleeping time was increased by approximately 40 percent.

Daniel and Bratt (1974) also found that DEHP was extensively metabolized after oral administration, the principal metabolites being identified as the acid, alcohol and ketone resulting from ω- and (ω-1)-oxidation of mono-2-ethylhexyl phthalate. DEHP was rapidly hydrolysed to the monoester by pancreatic lipase.

Williams and Blanchfield (1974) studied the retention, excretion and metabolism of di-(2-ethylhexyl) phthalate administered orally to the rat. There was only limited accumulation of DEHP-7-^{14}C by the male rat whether it was given as a single dose or fed as part of a diet. The adipose tissue was the only tissue or organ which consistently contained radioactivity, presumably as unchanged DEHP-7-^{14}C. In a 15-day feeding study, with a diet containing 0.1 percent of DEHP -7-^{14}C, the adipose tissue accumulated radioactivity equivalent to concentrations from 6 to 9 ppm of DEHP. Radioactivity was also detected in kidney, liver, testes, skeletal muscle, lungs and heart but much of this was probably due to DEHP-7-^{14}C consumed during the last 24 to 48 hours of the study.

Virtually all of the ingested DEHP-7-^{14}C was excreted in the urine or feces within 48 hours. No breakdown of DEHP-7-^{14}C to $^{14}CO_2$ was detected. The extent of metabolism and the pathway of excretion were found to be dependent on the magnitude of the phthalate ingestion. With a large single dose, 30 to 50 percent of the radioactivity was excreted in the feces, mostly as unchanged DEHP-7-^{14}C plus some 5 to 10 percent of an unknown metabolic product. The urine contained 4 percent of mono-2-ethylhexyl phthalate-7-^{14}C and at least seven other radioactive metabolic products in roughly equal concentration. Hydrolysis of the urine gave only phthalic acid-7-^{14}C, indicating that metabolism of DEHP-7-^{14}C did not involve modification or substitution of the aromatic ring.

When low levels of DEHP-^{14}C were fed in the diet 90 to 97 percent of the radioactivity was excreted in the urine with 2 to 5 percent of unchanged DEHP-7-^{14}C excreted in the feces. Metabolic products were excreted in the feces with a diet containing 0.2 percent of DEHP-7-^{14}C but with a diet containing only 10 ppm of DEHP-7-^{14}C all metabolic products were excreted in the urine. Analysis of the urine of rats fed a diet containing 0.1 percent DEHP-7-^{14}C showed no mono-2-ethylhexyl phthalate but did show other metabolic products similar to those of the single dose experiment, with some changes in the ratios of these products (Williams and Blanchfield, 1974). Hydrolysis of the urine gave only phthalic acid-7-^{14}C.

Williams and Blanchfield (1975) also studied the retention, distribution, excretion, and metabolism of dibutyl phthalate-7-^{14}C in the rat. Of a single oral dose 80 to 90 percent was metabolized and excreted in the urine within 48 hours. Phthalic acid, monobutyl phthalate, mono-3-hydroxybutyl

phthalate, and mono-4-hydroxybutyl phthalate were identified as metabolites in the urine. Rats fed for 12 weeks a diet containing dibutyl phthalate at 1 g/kg of feed did not accumulate either dibutyl phthalate or mono-butyl phthalate in tissues or organs.

Tanaka et al. (1975) studied the elimination, distribution and metabolism of ^{14}C-labelled di-(2-ethylhexyl) phthalate (DEHP) in the rat. About 80 percent of the dose was excreted in the urine and feces in 5 to 7 days following intravenous or oral administration. Excretion in the urine was generally slightly greater than that in the feces. After intravenous administration of ^{14}C-labelled DEHP the radioactivity was preferentially localized in the liver for a short period. Delayed excretion of DEHP was observed in particular in adipose tissue.

After oral dosing no significant retention occurred in organs and tissues after 5 to 7 days.

Radioactivity measurements showed that affinity was lowest for testicles and brain regardless of whether ^{14}C-labelled DEHP was administered orally or intravenously.

Orally ingested DEHP was excreted unchanged in the feces and four major metabolites were detected in the urine (Tanaka et al., 1975).

Ioku et al. (1975) reported that ^{14}C-labelled dimethyl phthalate and diethyl phthalate were rapidly absorbed following administration to mice and rats and most of them were excreted in urine and feces in 12 hours. The maximum concentrations in blood and in organs were attained at 20 minutes. The kidney had the highest concentration, followed by the liver and fat tissues. Dimethyl phthalate was excreted in urine (90.2 percent) and in feces (4.3 percent). Diethyl phthalate was excreted in urine (80.5 percent) and in feces (3.0 percent).

Singh et al. (1975) administered ^{14}C-di-(2-ethylhexyl) and ^{14}C-diethyl phthalates intraperitoneally to pregnant rats on either day 5 or day 10 of gestation. Rats were sacrificed at 24-hour intervals starting on days 8 and 11, respectively. Samples of maternal blood, fetal tissue, amniotic fluid, and placenta (where possible) were obtained. The reduction in the concentrations of ^{14}C from these samples as a function of time were found to fit first-order

excretion curves from which the half-lives for both phthalate compounds were calculated; the average for di-(2-ethylhexyl) phthalate was about 2.33 days and that for diethyl phthalate was about 2.22 days.

Ioku et al. (1976) found that ^{14}C-labelled dibutyl phthalate (DBP) and di-(2-ethylhexyl) phthalate (DEHP), administered orally to rats and mice, were rapidly absorbed and excreted in urine and feces within 48 hours. In blood plasma and in various organs the maximum concentrations of DBP were observed at 20 to 30 minutes; the maximum concentrations of DEHP were observed after 2 to 4 hours. The concentrations of DBP in tissues decreased in the order: liver>fat>spleen. The concentration of DEHP was highest in the liver. Both phthalates given to rats were from 30.6 to 43.5 percent excreted in the urine and from 20.0 to 22.0 percent excreted in the feces. Ioku et al. (1976) also reported that the amounts of DBP and DEHP absorbed by fetuses were approximately the same as the amounts accumulated in the fat.

Chu et al. (1978) studied the absorption, distribution and metabolic excretion of ^{14}C-mono-2-ethylhexyl phthalate (MEHP) in the rat. The ester was readily absorbed from the gastro-intestinal tract and the highest blood concentration occurred approximately 30 minutes after administration. Radioactivity following intravenous administration of ^{14}C-MEHP was rapidly distributed in all tissues, with the highest levels occurring in the liver, kidney and urinary bladder. Excretion of MEHP was rapid; approximately 80 percent of the dose was eliminated 24 hours after oral administration. In the excreta, 72 percent of the radioactivity was found in the urine and 8 percent in feces. After oral administration MEHP was extensively metabolized and the major urinary metabolites were identified as an alcohol, a ketone and an acid resulting from side-chain oxidation of MEHP. A trace of phthalic acid was also identified.

Waddell et al. (1977) determined the distribution in mice of intravenously administered plasma solutions of ^{14}C-labelled di-(2-ethylhexyl) phthalate (DEHP) by whole-body autoradiography. Plastic strips containing ^{14}C carbonyl-labelled DEHP were immersed in sterile mouse plasma for 78 days at 22°C. The plastic strips were the polyvinyl chloride formulation used for blood bags. One millilitre of the plasma, containing 2.293 µg of (^{14}C) DEHP, was injected intravenously without any further preparation into adult male mice of

the CD-1 strain. Five conventional mice were frozen by immersion in dry ice-hexane after light ether anesthesia at 1, 3, 9 and 24 hours and 7 days of injection. In addition, two conventional mice were anesthetized with phenobarbital and their renal pedicles were ligated before receiving the solution of (^{14}C) DEHP; they were frozen at 1 and 3 hours after injection. Five CD-1 germ-free mice were also frozen at 1, 3, 9 and 24 hours and 7 days after the injection; they were maintained germ-free until frozen. The mice were processed for whole-body autoradiography without allowing the tissues to thaw or contact any solvents. Autoradiography of whole-body sagittal sections taken at least every 200 μm through the left half of each animal revealed a rapid accumulation of radioactivity in the kidney and liver, with rapid excretion into urine, bile, and intestine. The compound was rapidly eliminated by the kidney and liver; there was no evidence of retention in any tissues in the body. There was no accumulation in spleen or lung.

Lake et al. (1977) made a study of the in vitro hydrolysis of dimethyl, diethyl, di-n-butyl, di-n-octyl, di-(2-ethylhexyl), and dicyclohexyl phthalates by both hepatic and intestinal preparations from various species. Hepatic preparations from the rat, baboon, and ferret hydrolyzed each of the phthalate diesters to their corresponding monoester derivatives. Additionally, intestinal preparations from the three animal species and from man also catalyzed the monohydrolysis of phthalate diesters. These results thus showed a species similarity in the metabolism of phthalate diesters between man, a rodent, a nonrodent, and a nonhuman primate species. Furthermore, the results suggested that orally ingested phthalate diesters would most probably be absorbed from the gut of the rat, baboon, ferret, and man primarily as the corresponding monoester derivatives.

2. Essentiality and Biological Role

There appears to be no evidence that phthalate esters are in any way essential for nutrition or that they have any particular biological role.

3. Acute Toxicity

Several excellent reviews of the toxicity of phthalate esters (Leah, 1977; Peakall, 1975; Autian, 1973; Krauskopf, 1973; Gesler, 1973; Hugos, 1972a; and Fassett, 1967) have been published. The low acute toxicity of phthalates is apparent from the values of LD_{50} shown in Tables 29, 30, 31 and 32.

TABLE 29

Acute Toxicities of Phthalates[a]

Phthalate	Species	Route	LD_{50}	Reference
Dimethyl	Mouse	oral	7.2 mL/kg	Draize et al. (1948)
	Mouse	i.p.	1.6 g/kg	Calley et al. (1966)
	Mouse	i.p.	2.4 mL/kg	Hodge et al. (1942)
	Mouse	i.p.	3.6 g/kg	Karel et al. (1947)
	Rat	oral	6.9 mL/kg	Draize et al. (1948)
	Rat	i.p.	3.4 mL/kg	Singh et al. (1972)
	Rabbit	oral	4.4 mL/kg	Draize et al. (1948)
	Rabbit	dermal	>10 mL/kg	
	Guinea pig	oral	2.4 mL/kg	
	Chicken	oral	8.5 mL/kg	
Diethyl	Mouse	i.p.	2.8 g/kg	Calley et al. (1966)
	Mouse	i.p.	2.75 g/kg	Karel et al. (1947)
	Rat	i.p.	5.1 mL/kg	Singh et al. (1972)
	Rat	oral	8.2 mL/kg	Tyson (1972)
	Rabbit	oral	1.0 g/kg	Kemp (1934)
	Rabbit	i.v.	0.1 g/kg	
Dibutyl	Mouse	oral	<13.0 g/kg	Bourne et al. (1968)
	Mouse	i.p.	4.0 g/kg	Calley et al. (1966)
	Mouse	i.p.	21.5 g/kg	Maslenko (1968)
	Mouse	i.p.	7 mL/kg	Elizarova (1961)
	Mouse	i.p.	5.5 mg/kg	Hodge et al. (1942)
	Mouse	i.p.	4.1 g/kg	Karel et al. (1947)
	Rat	oral	23 g/kg	Radeva and Dinoeva (1966)
	Rat	oral	17.9 g/kg	Maslenko (1968)
	Rat	oral	13.8 mL/kg	Homrowski and Nikonorow (1959)
	Rat	oral	>20 g/kg	Lehman (1955)
	Rat	oral	8 g/kg	Smith (1953)
	Rat	oral	8 g/kg	Bourne et al. (1968)
	Rat	inh.	0.7-0.9 mg/l	Spasovski (1964)
	Rat	s.c.	<6.2 g/kg	Kowalski and Bassendowska (1965)
	Rat	i.p.	4.5 g/kg	
	Rat	i.p.	10 mL/kg	Elizarova (1961)
	Rat	i.p.	3.05 mL/kg	Singh et al. (1972)
	Rat	i.p.	8.3 mL/kg	Homrowski and Nikonorow (1959)
	Bluegill	LC_{50}[b]	1.23 mg/l	Mayer and Sanders (1973)
	Channel catfish	LC_{50}[b]	3.72 mg/l	
	Scud	LC_{50}[b]	7.00 mg/l	
Diisobutyl	Mouse	oral	>12.8 g/kg	Fassett (1967)
	Mouse	i.p.	4.5 g/kg	Calley et al. (1966)
	Rat	oral	20-25 g/kg	Fassett (1967)
	Rat	i.p.	3.75 mL/kg	Singh et al. (1972)
	Guinea pig	dermal	10 mL/kg	Fassett (1967)

TABLE 29 (Continued)

Acute Toxicities of Phthalates[a]

Phthalate	Species	Route	LD_{50}	Reference
Dihexyl	Rat (male)	oral	29.6 mL/kg	Krauskopf (1973)
	Rat (female)	oral	38.9 mL/kg	Krauskopf (1973)
	Rat	oral	29.6 g/kg	Smyth et al. (1954)
	Rabbit	dermal	20 mL/kg	
Di(2-ethylhexyl)	Mouse	oral	>128 g/kg	Hodge (1943)
	Mouse	i.p.	14.2 g/kg	Galley et al. (1966)
	Mouse	i.p.	>75 g/kg	Gesler and Kartinos (1970)
	Rat	oral	>26 g/kg	Fassett (1967)
	Rat	oral	30.6 g/kg	Shaffer et al. (1945)
	Rat	oral	>34 g/kg	Hodge (1943)
	Rat	i.p.	>50 mL/kg	Singh et al. (1972)
	Rabbit	oral	33.9 g/kg	Shaffer et al. (1945)
	Guinea pig	dermal	>10 g/kg	Fassett (1967)
	Mouse	oral	>13 g/kg	
Dioctyl	Rat	oral	45.1 mL/kg	Homrowski and Nikonorow (1959)
	Rat	oral	30 g/kg	Radeva amd Dinoeva (1966)
	Rat	i.p.	46 mL/kg	Hodge et al. (1942)
	Rat	i.p.	50 mL/kg	Homrowski and Nikonorow (1959)
	Rat	i.p.	>50 mL/kg	Singh et al. (1972)
	Guinea pig	dermal	>5 mL/kg	Fassett (1967)
Dicapryl	Mouse	i.p.	14.2 g/kg	Calley et al. (1972)
Diisonoyl	Rat	oral	>10 g/kg	Livingston (1971)
Diisodecyl	Rat	oral	>64 mL/kg	Smyth et al. (1954)
Ditridecyl	Rat	oral	>64 mL/kg	
Butylbenzyl	Mouse	i.p.	3.2 g/kg	Calley et al. (1972)
	Rat	i.p.	1.8 g/kg	Mallette (1952)
	Rat	oral	4.0 g/kg	
Dialkyl 79 phthalate	Mouse	oral	>20 g/kg	Gaunt et al. (1968)
	Mouse	i.p.	>20 g/kg	
	Rat	oral	>20 g/kg	
	Rat	i.p.	>20 g/kg	
	Rat	i.p.	44 g/kg	Elizaroya (1961)
	Rat	oral	13.3 mL/kg	
	Mouse	oral	7 mL/kg	
Dialkyl 9-11 phthalate	Rat	oral	>20 mL/kg	Brown et al. (1970)
	Mouse	oral	>20 mL/kg	

TABLE 29 (Continued)

Acute Toxicities of Phthalates[a]

Phthalate	Species	Route	LD_{50}	Reference
Dimethoxyethyl	Mouse	oral	3.2-6.4 g/kg	Fassett (1967)
	Mouse	i.p.	2.51 g/kg	Calley et al. (1966)
	Rat	oral	>4.4 g/kg	Fassett (1967)
	Rat	i.p.	3.7 mL/kg	Singh et al. (1972)
	Guinea pig	oral	1.6-3.2 g/kg	Fassett (1967)
	Guinea pig	dermal	>10 mL/kg	Fassett (1967)
Diallyl	Mouse	i.p.	0.7 g/kg	McOmie (1949)
	Mouse	i.p.	0.6 mL/kg	McOmie and Anderson (1947)
	Rat	oral	0.8-1.7 g/kg	McOmie (1949)
	Rabbit	oral	1.7 g/kg	McOmie (1946)
	Rabbit	dermal	3.4 mL/kg	McOmie (1949)
Butyl carbobutomethyl	Rat	oral	14.6 mL/kg	Patty (1967)
	Rat	i.p.	6.89 g/kg	Singh et al. (1972)

[a]Some additional information on mixed esters is given in Krauskopf (1973).

[b]Twenty-four hours.

These data are from Peakall (1975).

TABLE 30

Acute Oral Toxicity of Phthalates

Phthalate	Species	LD_{50}	Reference
Symmetrical			
Dimethyl	Guinea pig	2.4 g/kg	(8)
	Mouse	7.2 g/kg	(8)
	Rabbit	4.4 g/kg	(8)
	Rat	6.9 g/kg	(8)
	Rat	6.7 g/kg	(9)
	Rat	6.8 g/kg	(10)
Diethyl	Rat	8.2 mL/kg	(11)
Dibutyl	Rat	>20 g/kg	(8)
	Rat	ca. 8 g/kg	(12)
	Rat	8-10 g/kg	(7)
	Rat	10 g/kg	(7)
Di-n-butyl	Rat	12.6 g/kg	(13)
Di-n-hexyl	Rat (males)	29.6 mL/kg	(9)
	Rat (females)	38.9 mL/kg	(9)
Dicyclohexyl	Rat	30. mL/kg	(7)
Diisooctyl	Rat	22.6 mL/kg	(13)
Di-2-ethylhexyl	Guinea pig	26.3 g/kg	(9)
	Mouse	34.0 mL/kg	(9)
	Rabbit	33.9 g/kg	(14)
	Rat	30.6 g/kg	(14)
	Rat	34.3 mL/kg	(9)
Diisononyl	Rat	>10 g/kg	(15)
Diisodecyl	Rat	>64 mL/kg	(16)
Ditridecyl	Rat	>64 mL/kg	(16)
Coesters of alcohol mixtures			
Butyl, octyl	Rat	>63 mL/kg	(13)
Butyl, decyl	Rat	20.8 mL/kg	(17)
Hexyl, decyl	Rat	49.4 mL/kg	(17)
n-Hexyl, n-octyl, n-decyl	Rat	45.2 mL/kg	(13)

TABLE 30 (Continued)

Acute Oral Toxicity of Phthalates

Phthalate	Species	LD_{50}	Reference
Heptyl, nonyl	Mouse	>19.3 g/kg	(18)
	Rat	>19.3 g/kg	(18)
Heptyl, nonyl, undecyl	Mouse	>20 g/kg	(18)
	Rat	>20 g/kg	(18)
	Rat	>64 g/kg	(13)
Octyl, decyl	Rat	45.2 mL/kg	(17)
	Rat	>63 mL/kg	(13)
2-ethylhexyl, benzyl	Rat	60.3 g/kg	(19)
Nonyl, undecyl	Mouse	>19.7 g/kg	(18)
	Rat	>19.7 g/kg	(18)
Related diesters			
Di-2-ethylhexyl tetrahydrophthalate	Rat	>114 mL/kg	(13)
Di-2-ethylhexyl hexahydrophthalate	Rat	>63 g/kg	(13)
Di-2-ethylhexyl isophthalate	Rat	17.3 mL/kg	(16)
Diisodecyl isophthalate	Rat	>64 mL/kg	(16)
Diisodecyl tetrahydro-4, 5-epoxyphthalate	Rat	>63 mL/kg	(13)

These data are from Krauskopf (1973).

TABLE 31

Acute Toxicity of Phthalate Esters: LD_{50} in Animals

Compound	Animal	Route	LD_{50} g/kg	Reference
Dimethyl phthalate	Mouse	Oral	7.2	(5c)
	Mouse	IP	3.6	(5c)
	Mouse	IP	1.58	(13)
	Rat	Oral	2.4	(5c)
	Rat	IP	3.38[a]	(14)
	Guinea pig	Oral	2.4	(5c)
	Rabbit	Dermal	10.0[a]	(5c)
Dietyl phthalate	Mouse	IP	2.8	(5c)
	Mouse	IP	2.8	(13)
	Rat	IP	5.06[a]	(14)
	Rabbit	Oral	1.0	(5c)
Dimethoxyethyl phthalate	Mouse	Oral	3.2-6.4	(5c)
	Mouse	IP	2.51	(13)
	Rat	Oral	4.4	(5c)
	Rat	IP	3.7	(13)
	Guinea pig	Oral	1.6-3.2	(5c)
	Guinea pig	Dermal	10.0[a]	(5c)
Diallyl phthalate	Mouse	IP	0.7	(5c)
	Rat	Oral	1.7	(5c)
	Rabbit	Oral	1.7	(5c)
	Rabbit	Dermal	3.4[a]	(5c)
Dibutyl phthalate	Mouse	IP	4.0	(13)
	Rat	IP	3.05[a]	(14)
	Rat	IM	8.0	(5c)
	Rabbit	Dermal	20.0[a]	(5c)
Diisobutyl phthalate	Mouse	Oral	12.8	(5c)
	Mouse	IP	4.50	(13)
	Rat	IP	3.75[a]	(14)
	Guinea pig	Dermal	10.0[a]	(5c)
Butyl carbobutoxymethyl phthalate	Rat	Oral	14.6[a]	(5c)
	Rat	IP	6.89	(14)
Dihexyl phthalate	Rat	Oral	30.0	(5c)
	Rabbit	Dermal	20.0[a]	(5c)
Dioctyl phthalate	Mouse	Oral	13.0	(5c)
	Rat	IP	50.0[a]	(14)
	Guinea pig	Dermal	5.0[a]	(5c)

TABLE 31 (Continued)

Acute Toxicity of Phthalate Esters: LD_{50} in Animals

Compound	Animal	Route	LD_{50} g/kg	Reference
Di-2-ethylhexyl phthalate	Mouse	IP	14.2	(13)
	Rat	Oral	26.0	(5c)
	Rat	IP	50.0[a]	(14)
	Rabbit	Oral	34.0	(5c)
	Guinea pig	Dermal	10.0	(5c)
Butylbenzyl phthalate	Mouse	IP	3.16	(13)
Dicapryl phthalate	Mouse	IP	14.2	(13)
Dinonyl phthalate	Rat	Oral	2.00	(5c)
Dibutyl (diethylene glycol bisphthalate	Mouse	Oral	11.2	(15)
	Mouse	IP	~11.2	(15)
	Rat	Oral	11.2	(15)
	Rat	IP	~11.2	(15)
Dialkyl 79 phthalate	Mouse	Oral	>20.00	(16)
	Rat	IP	>20.00	(16)

[a]LD_{50} in ml/kg.

These data are from Autian (1973).

TABLE 32

Acute Median Lethal Doses (LD_{50}) of Phthalate Esters

Phthalate Ester	Animal Species	Route of Administration[a]	LD_{50} g/kg	Reference
Dimethyl	Mouse	IP	<0.97-2.86	(5-7)
Diethyl	Mouse	IP	<1.11-2.83	(6,7)
Di-n-propyl	Mouse	IP	<1.25	(7)
Diisopropyl	Mouse	IP	<1.25	(7)
Di-n-butyl	Mouse	IP	<1.39-5.76	(5-7)
		IM	>8	(8)
		PO	ca.8	(8)
	Rat	PO	23.0	(9)
Diisobutyl	Mouse	IP	4.5	(6)
Di-n-hexyl	Rat	PO	29.6	(10)
Di-2-ethylhexyl	Mouse	IP	14.19->128	(6,11,12)
	Rat	IP	>23.8->70	(12-14)
		PO	30.6->60	(12-14)
	Rabbit	IP	31	(13)
		PO	33.9	(14)
Dialkyl (79)	Mouse	IP	>20	(15)
		PO	>20	(15)
	Rat	IP	>20	(15)
		PO	>20	(15)
Di-n-capryl	Mouse	IP	14.19	(6)

[a]IP = intraperitoneal; IM = intramuscular; PO = by mouth.

These data are from Gesler (1973)

Krauskopf (1973) has noted that phthalic acid, which has an LD_{50} of 7.9 mL/kg in the rat, and various alcohols that may be used as plasticizers or reacted with phthalic acid to produce phthalate esters, appear to be more toxic than the phthalate esters.

4. Carcinogenesis

Reviews of the literature on the chronic toxicity of phthalate esters (Withey, 1977; Leah, 1977; Peakall, 1975; Krauskopf, 1973; Autian, 1973; Gesler, 1973; Hugos, 1972a; and Fassett, 1967) have provided no evidence that any phthalates are carcinogens (but see p. 111 for a note added in press).

5. Studies of Reproduction

Onda et al. (1974; Omori, 1976) examined for three generations the effects of di-(2-ethylhexyl) phthalate (DEHP) and dibutyl phthalate (DBP) on different strains of mice. Dietary administration of DEHP and DBP at levels of 10 and 100 mg/kg day increased the incidence of renal cysts in the first two generations of descendants. Onda et al. assumed that the phthalate esters crossed the placental barrier to cause the renal damage to the fetuses. Di-(2-ethylhexyl) phthalate was found to cause a higher incidence of kidney disorders than DBP. Some strains of mice were more susceptible than others.

6. Teratogenesis

Piekacz (1971) studied the effects of long-term peroral administration of two phthalates on fertility and fetal development in rats. The phthalates were administered daily by stomach tube at doses of either 0.34 g/kg or 1.7 g/kg of dioctyl phthalate, which may actually have been di-(2-ethylhexyl) phthalate, or either 0.12 g/kg or 0.60 g/kg of dibutyl phthalate. These doses were said to correspond to one or five percent of the LD_{50} values, which evidently were assumed to be about 34 g/kg for dioctyl phthalate and about 12 g/kg for dibutyl phthalate. The doses were given for a period of three months before conception and throughout the period of pregnancy, i.e., for 21 days after fertilization occurred. The animals which received the higher dose of dibutyl phthalate showed the smallest incidence of live fetuses. Statistical analysis showed, at the confidence level of 0.05, a significant decrease of the mean weight of fetuses in female rats that were given either dose of dioctyl phthalate or the higher dose of dibutyl phthalate during pregnancy. For all groups of rats given

either phthalate during pregnancy and the group given the higher dose of dibutyl phthalate before conception a statistically significant difference was found in the mean weight of placentas. No impairment of ossification was noted in the fetuses of the treated females.

Singh et al. (1972) undertook a teratogenic study in rats using the following phthalates: dimethyl-, dimethoxyethyl-, diethyl-, dibutyl-, diisobutyl-, butyl carbobutoxymethyl-, dioctyl-, and di-(2-ethylhexyl)-. The first six of these phthalates, having acute intraperitoneal LD_{50} values below 10 mL/kg, were administered to rats at doses representing one-tenth, one-fifth and one-third of the acute LD_{50} dose on the 5th, 10th and 15th days of gestation; the two less toxic compounds were injected at levels of 5 and 10 mL/kg. The number of corpora lutea ranged from 52 to 65 per group of five rats, with no apparent distribution according to treatment. Embryo-fetal toxicity ranged from 0 percent to a high of 98.2 percent. Fetal malformations ranged from 0 to 100 percent, for both gross and skeletal abnormalities, with skeletal defects generally being more common. Fetuses from all phthalate-treated groups were smaller ($p \leq 0.01$) than the untreated controls. Anophthalmia, twisted hind legs and absence of tail were the most common gross abnormalities, while elongated and fused ribs and abnormal skull bones were the most common deformities found in skeletal specimens. The results of this study have been summarized by Leah (1977), Peakall (1975), Autian (1973), and by Dillingham and Autian (1973).

7. Mutagenesis

Dillingham and Autian (1973) reported the unpublished results of an investigation by Singh, Lawrence and Autian of the possible mutagenicity of two phthalate esters in mice. The mutagenic effects of di-(2-ethylhexyl) phthalate (DEHP) and dimethoxyethyl phthalate (DMEP) were investigated by intraperitoneal administration of a single dose of the respective undiluted esters to male (ICR) mice immediately prior to the initiation of a mating period in which 10 treated males were mated (two females per male) each week for 12 weeks. The dose levels employed were one-third, one-half, and two-thirds of the acute LD_{50} dose. A parallel untreated mating group was maintained as a control (240 matings). Shortly before expected parturation, the pregnant females were sacrificed and the uterine horns exposed surgically to permit recording of the numbers of corpora lutea, total numbers of implantations, preimplantation losses (by

difference between those two parameters), resorption sites (early fetal deaths), dead fetuses (late fetal deaths), and viable fetuses. The results were consistent with the finding of significant dominant lethal mutation for both compounds. The mutagenic effect of DEHP was significantly greater than that of DMEP, in contrast to the teratogenic effects of those compounds. More complete results have appeared in research papers by Singh et al. (1974a,b).

Shahin and von Borstel (1977) tested dibutyl phthalate for mutagenic activity by a reversion analysis of Sassharomyces cerevisiae, strain XV 185-14C. The compound was tested for its ability to induce reversions using three different loci: lys1-1, hys1-7, and hom3-10 in the absence and in the presence of metabolic conversion. Shahin and von Borstel found that dibutyl phthalate was not active in the XV185-14C assay system of S. cerevisiae.

8. Allergenesis

There are no published reports which show that phthalate esters are allergenic (Wei et al., 1978).

9. Other chronic toxicity and clinical effects

The chronic toxicity of phthalate esters has been reviewed by many authors including Withey (1977), Leah (1977), Peakall (1975), Krauskopf (1973), Gesler (1973), Autian (1973), Hugos (1972a) and Fassett (1967). Phthalate esters have been found to have a very low order of toxicity when administered orally to animals (Krauskopf, 1973), as is shown in Tables 33 to 36. Summaries of chronic toxicity data are shown in Tables 37 and 38.

Lawrence et al. (1975; cf. Lawrence et al., 1974) subjected a number of phthalate esters to various biological tests for acute, short-term, and chronic toxicity. In their chronic toxicity studies a series of doses was injected ip into groups of ten male mice, five days per week (Monday through Friday). At the end of each week an apparent LD_{50} was calculated. The experiment was continued until the apparent LD_{50} remained constant for three consecutive weeks with a minimum of ten weeks' treatment, at which time it was assumed that a phthalate had reached its chronic toxicity value. The results for eight phthalate esters are shown in Table 39 in which acute LD_{50} values and cumulative toxicity factors (acute LD_{40}/chronic LD_{50}) are shown.

TABLE 33

Summary of Ingestion Studies with Dibutyl Phthalate

Reference	Species	Dose	Period	Observation and Conclusions
(23)	Rats	2.5 mg/kg/day	6 months	No effect; recommended maximum level of 2 mg/l in reservoir due to toxicity; taste and odor threshold at 5 mg/l.
(7)	Rats	4g/kg	Single dose	Zero died
		8 g/kg	Single dose	4/9 died LD_{50} = 8-10 g/kg
		16 g/kg	Single dose	6/6 died
(7)	Rats	0.01%/day	1 year	No effect
		0.05%/day	1 year	
		1.25%/day	1 year	50% died in 1 week; no lesions observed
(7)	Rats	5 mL/kg[a]	Single dose	All lived LD_{50} = 10 mL/kg; rabbits and
		15 mL/kg[a]	Single dose	All died; dogs LD_{50} similar to rats
		0.5 mL/kg[b]	1 year	Nothing abnormal
		1.0 mL/kg[b]	1 year	
(7)	Rats	100 mg/kg/day for 5 generations, also some for 21 months		No carcinogenic or
		300 mg/kg/day for 3 generations, also some for 21 months		poisonous effects
		500 mg/kg/day for 3 generations, also some for 15 months		
(7)	Human	10 g (accident for laxative)	Single dose	Nausea, vertigo, hepatitis, and toxic nephritis; released after 14 days in hospital.
(12)	Rats	4 g/kg	Single dose	Deaths 0/3 (no lethal effects)
		8 g/kg	Single dose	4/9
		16 g/kg	Single dose	6/6
		32 g/kg	Single dose	6/6
(12)	Rats	0.25%[c]	1 year	No effect[d]
		1.25%	1 year	50% fatal in 1 week, other 50% similar to controls. No gross or microscopic changes; DBP metabolized by pancreatic lipases[d]

[a]Administered at 50% in olive oil.
[b]Administered at 50% solution, 2 times/week.
[c]350-110/mg/kg body weight.
[d]Acute oral lethal doses = 8 g/kg.

These data are from Krausdopf (1973).

TABLE 34

Summary of Ingestion Studies with Di-2-ethylhexyl Phthalate

Reference	Species	Dose	Period	Observation and Conclusions
(13)	Rats	0.13% in diet	2 yr	No effect
	Dogs	0.13%	1 yr	No effect
(23)	Rats	0.5 mg/kg/day	6 mo	No effect; recommended maximum level of DOP tolerable in water (reservoir) is 2.5 mg/l. based on odor and taste.
(5)	32 Male rats[a]	0.4% of diet	2 yr	
	32 Female rats[a]	0.13%	2 yr	No effect; no-effect level > 0.13, > 0.4% (> 0.06 g/kg/day, < 0.29/kg/day)
		0.04%	2 yr	
		0.0.%	2 yr	
	80 Filial rats[a]	0.4% of diet	1 yr	
		0.0%	1 yr	No effect
(5)	Guinea pigs (males and females)	0.0%	1 yr	
		0.4%	1 yr	No effect on liver and kidney weights of males and kidney weights of females, but liver weights of females were 13% > controls (unexplainable).
		0.13%	1 yr	No effect up to and involving 0.13% DOP in diet of guinea pigs close to 0.06 g/kg/day.
(5)	8 Dogs (14-17 months old)	0.03 mL/kg/day, 4wk	1 yr total	No effect; approximate no-effect level = 0.06 ml/kg/day
		0.06 mL/kg/day, 48 wk	1 yr total	
(5)	1 Dog	0.06 mL/kg/day	15 wk	
		0.09 mL/kg/day	34 wk	

TABLE 34 (Continued)

Summary of Ingestion Studies With Di-2-ethylhexyl Phthalate

Reference	Species	Dose	Period	Observation and Conclusions
(24)	43 Male rats 43 Female rats	0.0% of diet 0.1% 0.5%	3 mo 6 mo 12 mo 24 mo	Mortality: no effect due to DOP Body weight: no effect due to DOP Food intake: no effect for first year; but 0.5% group ate only 75% of control group during second year No effect 0.4%, Carpenter's rats ≈ 0.2 g/kg/day = 200 mg/kg 0.1% in rats for 2 years Organ weights: no difference, except for slight increase of liver and kidney with 0.5% diet Pathology: no effect
(24)	2 dogs	5 g/kg/day, stomach tube 0.1 g/kg/day in diet	14 wk 14 wk	Mild toxic changes at 14 weeks, 0.1 g/kg/day gave no effect at 14 weeks, but it is pointed out that Carpenter (5) had found 0.09 mL/kg/day to give toxic changes in liver and kidney after 1 year feeding. Not harmful in industry or food wraps.
(22)	Mice	34.5 g/kg	Single dose	No fatalities
(14)	Rats	79.5 g/kg	Single dose	Killed 8/10 rats
(14)	5 rats (male, weighing 120-150 g)	3.0% (1.9 g/kg/day) 1.5% (0.9 g/kg/day) 0.75 (0.4 g/kg/day) 0.375%(0.2 g/kg/day) 0.0% (0 g/kg/day)	90 days 90 days 90 days 90 days 90 days	Slight slowing of weight gain No effect
(14)	2 Humans (adult males)	10g 5 g	Single dose Single dose	Diarrhea Urinalyses gave 4.5% of the dose No effect within 24 hr
(14)	2 Dogs	2 g/kg	Single dose	Urinalyses: 2.0-4.5% of dose in 3 days

TABLE 34 (Continued)

Summary of Ingestion Studies with Di-2-ethylhexyl Phthalate

Reference	Species	Dose	Period	Observation and Conclusions
(14)	5 Rabbits	2 g/kg	Single dose	Urinalyses for 3 days: recovered 26-65% of dose (average = 42%)
(25)	Rats	61 mL/kg	Single dose	0/10 no effect; DOP very low order of toxicity. 34 g/kg gave no deaths.
(22)	Rats	25 g/kg tube 110 g/kg, tube	Single dose Single dose	No effect Diarrhead
(26)	Rats	15.8 g/kg	Single dose	Nonlethal
(13)	Rats	0 0.1% of diet 0.5% of diet	 3 mo 6 mo	Weights of all organs and bone marrow measured; only liver and kidney weights showed slight gains at 3 and 6 months. No clear-cut evidence of toxic effects, but 6-month specimens indicated that changes in bladder of 20% of species may be due to diet.
(6)	Rats	0 0.1% of diet 0.5% of diet	3 mo 6 mo 12 mo 24 mo	Control group had 44/46 fatality; 2 years is maximum period useful for rats ΔWeight: all same; all organs: no change. Liver and kidney definitely not > controls. Lungs, brain, stomach, heart, spleen, testes, also weighed Pathological: test animals similar to controls (aging change)
(6)	Rats	6/mL/kg, tube	Single dose	10/10 survived > 7 days

TABLE 34 (Continued)

Summary of Ingestion Studies with Di-2-ethylhexyl Phthalate

Reference	Species	Dose	Period	Observation and Conclusions
(6)	Dogs	0.1 g/kg/day (female) 5.0 g/kg/day (male) 10.0 g/kg/day	14 wk 14 wk	No effect: slight loss of weight gain. Hematology: normal; Histological: normal; Urinalyses: no effect (on female only). At 10 g/kg, the dog refused to eat for 2 days

[a]Test started at 2 months age of rats.

[b]Equal to 0.0.5 - 0.08 g/kg/day.

[c]Equal to 0.3 - 0.4 g/kg/day.

[d]Reports DOP much less toxic than DCP (22).

These data are from Krauskopf (1973).

TABLE 35

Summary of Ingestion Studies with Various Phthalates

Phthalate	Reference	Species	Dose	Period	Observation and Conclusions
Dimethyl phthalate					
	(7)	Mice	1-4 g/kg	Single dose	No effect
	(7)	Dogs	0.7-1.4 g/kg	Single dose	No effect
Di (mixed heptyl, nonly) phthalate					
	(27)	Rats and mice (fasted 18 hr)	0[a] 0.125%[a] 0.25%[a] 0.5%[a] 1.0%[a]	90 days	1% level gave growth retardation to males; slight anemia in all at 0.25%, 0.5, 1.0% of diet; At 0.5, 1.0% kidney and liver weights increased; definitely no effect at 0.125%.
	(27)	Rats and mice (fasted 18 hr)	20 g/kg	Single dose, acute	Diarrhea
Santicizer 711 [(di(linear, C_7, C_9, C_{11} mixed alcohol) phthalate]					
	(26)	Rats	20 g/kg	Single dose	No effect; nontoxic
Diisononyl phthalate					
	(15)	Rats	10 g/kg 5 g/kg	Single dose Single dose	Oily fur Oily fur; no loss in weight gain rate; Symptoms gone after 7 days; LD_{50} >10 g/kg
	(15)	Rats (male and female)	0 mg/kg/day 50 mg/kg/day 150 mg/kg/day 500 mg/kg/day	13 wk 13 wk 13 wk 13 wk	 No effect Liver weight increased; slight loss in body weight gain rates

TABLE 35 (Continued)

Summary of Ingestion Studies with Various Phthalates

Phthalate	Reference	Species	Dose	Period	Observation and Conclusions
	(15)	4 Dogs (male and female)	0% of diet	13 wk	
			0.125%[b]	13 wk	No effect
			0.500%	13 wk	Questionable no effect (weight gain of liver)
			2.0%	2% for 8 wk increased to 4% for 9-13 wk	Increase in liver weight; loss in body weight; histologic changes in liver, gallbladder, spleen, and kidney
			4.0%		
Diisodecyl phthalate	(28)	Rats	30 ml/kg	Single dose	All survived
	(28)	Rabbits	30 ml/kg	Single dose	Minimum lethal dose calculated at 22.5-30 ml/kg
Diundecyl phthalate	(29)	Rats	15.8 g/kg	Single dose	Nonlethal; practically nontoxic
Dicyclohexyl phthalate	(7)	Rats	25% in olive oil	Single dose	None died at 24 hr; LD_{50} = 30 ml/kg; rabbits and dogs similar
			25% in olive oil	7 days	
	(7)	Rats	0.5 ml/kg	2 doses/wk, 32 wk	No effects
			1.0 ml/kg	2 doses/wk, 52 wk	
	(7)	Rats	5 mg/kg	4 generations, also one for 18 mo	No effect, not carcinogenic
			10 mg/kg		
			100 mg/kg		

TABLE 35 (Continued)

Summary of Ingestion Studies with Various Phthalates

Phthalate	Reference	Species	Dose	Period	Observation and Conclusions
	(30)	Rats	31.2 g/kg (33% in water)	2 doses in 1 day	All survived
			62.4 g/kg (33% in water)	4 doses in 2 days	All survived
	(30)	Rabbits	23.0 g/kg	2 doses in 1 day	All survived
			44.1 g/kg	4 doses in 2 days	All survived; no phthalate was absorbed in intestinal tract by any rats or rabbits tested.
Butyl benzyl phthalate	(31)	Rats	0.25% of diet	90 days	No effect
			0.50%	90 days	
			1.00%	90 days	
			1.50%	90 days	Mild loss of growth rate
			2.00%	90 days	Mild loss of growth rate No adverse hematologic effects No effect in urinalysis Liver weight gain for 1.00, 1.5, 2.0% animals No histopathologic effects
	(31)	Dogs	1.0% capsules[c]	90 days	No deaths. No effect on weight gain at 1.0 and 2.0%, 5.0% group gained less initially due to refusal to eat; capsules restored normal eating.
			2.0% capsules[c]	90 days	No effect found at all levels in hematological, urinalyses, liver and kidney functions
			5.0% capsules[c]	90 days	All functioning parts at end of test

[a]0,0.125, 0.25, 0.5, 1.0% equivalent to 0, 0.05-0.16, 0.1-0.34, 0.21-0.66, and 0.45-1.33 g/kg/day, respectively.
[b]0.125, 2.0, 4.0% equivalent to mean dose of 37 538, and 1340 (males) and 1075 (females) mg/kg/day, respectively.
[c]Wt-% of daily diet.

These data are from Krauskopf (1973).

TABLE 36

Acceptable Daily Intake (ADI) Values Calculated from Various Investigations

Phthalate	Species	Period, days	Maximum no-effect level, mg/kg/day	ADI, mg/kg[a]	Reference
Di-2-ethylhexyl	Rat	365	400	4.0	(24)
	Rat	730	80	8.0	(24)
	Dog	98	100	0.2	(24)
	Rat	90	200	0.4	(14)
	Dog	98	100	0.2	(6)
	Rat	365	>60, <200	>8.4, < 28 >0.6, < 2.0	(5)
	Guinea pig	365	ca. 0.6	ca. 0.6	(5)
	Dog	365	ca. 0.6	ca. 0.6	(5)
Dibutyl	Rat	365	350 - 110	3.5-1.1	(12)
	Rat	450	4.3	0.04	(7)
Diisononyl	Rat	91	150	0.3	(15)
	Dog	91	37	0.07	(15)
Heptyl nonyl	Rat	90	ca. 60	ca. 0.12	(27)
	Mouse	90	ca. 60	ca. 0.12	(27)

[a]ADI = N/F, where F = 500 for < 365-day period; 100 for ≥ 365-day period.

These data are from Krauskopf (1973).

TABLE 37

Summary of Chronic Toxicity Data on Phthalate Esters

Phthalate ester	Animal species	Number of animals in study		Study duration, weeks	No-effect level		Toxic signs[a]	Reference
		Controls	RX		% in diet	Mg/kg/day		
Dialkyl 79	Rat	30	120	13	0.125	60	Growth retardation, increased kidney and liver weight	(15)
Di-n-butyl	Rat	10	40	52	0.25	110-330	Death at 1.25%	(8)
Di-2-ethyl-hexyl	Rat	5	20	13	0.375	200	Growth retardation, testicular degeneration, tubular atrophy	(14)
	Rat	b	272	104	0.13-0.4	60-200	Growth retardation, increased kidney and liver weight	(23)
		86	172	to 104	0.1	40-80	Same	(13)
	Guinea pig	46	93	52	0.13	60	Increased liver weight in females only	(23)
	Dog	4	5	52	-	59	Fatty vacuolization and congestion in subcapsular area of liver and moderate kidney congestion	(23)
	Dog	0	2	14	-	100	Weight loss and cholecystitis reported in one dog	(13)

[a]At higher than no-effect level.

[b]Number not given but "approximate controls" were included in the study.

These data are from Gesler (1973)

TABLE 38

Summary of Toxicity Studies of Phthalate Esters

Species	Length of Experiment (days)	Doses mg/kg)	Observations	Maximum No-effect Level mg/kg/day	References
Di-2-ethylhexyl phthalate					
Rat	98 & 180	200	Liver & Kidney weight increased, growth retardation, histology normal	60 (organ weights normal)	Harris et al. (1956
Rat	365	400 & 200	Histopathology normal (Liver, kidney, etc.) lower body weight & food consumption		Carpenter et al. (1953)
Rat	730	400 & 200	Histopathology normal (Liver, kidney, etc.) lower body weight & food consumption	**	Carpenter et al. (1953)
Dog*	98	100	Histopathology of liver and kidney normal	60 (organ weights normal)	Carpenter et al. (1953)
Dog*	98	5000	cholecystitis	60 (organ weights normal)	Carpenter et al. (1953)
Rat	365	200	Growth retardation increased liver & kidney weight	60 (organ weights normal)	Carpenter et al. (1953)
Guinea Pig	365	60	Increased liver weight pathology normal		

TABLE 38 (Continued)

Summary of Toxicity Studies of Phthalate Esters

Species	Length of Experiment (days)	Doses mg/kg)	Observations	Maximum No-effect Level mg/kg/day	References
Di-2-ethylhexyl phthalate					
Dog	365	90	Fatty vacuoles of the liver and kidney congestion	60 (histology of liver & kidney normal)	
Rat	90	400	Retarded growth pathology normal	200 (organ weight normal)	Shaffer et al. (1945)
Dibutyl phthalate					
Rat	365	525-1600	50% of the treated group succumbed in the first week		Smith (1953)
Rat	365	110-350	Growth and survival rate normal	110 - 350	
Heptyl nonyl phthalate					
Rat	90	130-740	Increased liver and kidney weight, anemia	60	Gaunt et al. (1968)

*Only one dog was used.

**Not enough rats survived for statistical analysis.

TABLE 39

Chronic ip Toxicity of Phthalate Esters in Mice

Week no.	Apparent LD_{50} (mL/kg) by weeks							
	Dimethyl	Diethyl	Di-n-butyl	Diisobutyl	Di-n-octyl	Di-2-ethylhexyl	Butyl carbo-butoxymethyl	Bis(2-methoxyethyl)
(Acute LD_{50})	(3.35)	(2.87)	(3.41)	(3.84)	(67.18)	(38.35)	(6.27)	(3.57)
1	2.45	2.26	2.08	2.48	25.51	6.40	4.94	1.99
2	2.45	2.00	1.84	2.38	12.75	3.63	4.61	1.99
3	2.45	2.00	1.84	2.20	9.22	2.85	4.61	1.99
4	2.45	2.00	1.84	2.20	7.84	2.06	4.61	1.99
5	2.45	1.92	1.84	2.20	7.53	1.90	4.30	1.86
6	2.35	1.84	1.84	2.20	6.40	1.68	4.01	1.73
7	2.35	1.77	1.77	2.11	4.44	1.61	3.75	1.62
8	2.26	1.70	1.77	2.11	3.35	1.49	3.26	1.62
9	1.92	1.70	1.70	2.03	3.21	1.43	3.04	1.41
10	1.84	1.70	1.63	2.03	3.09	1.37	3.04	1.41
11	1.77	1.57	1.45	1.87	3.09	1.37	3.04	1.41
12	1.39	1.39	1.39	1.87	3.09	1.37	-	-
13	1.33	1.39	1.33	1.87	-	-		
14	1.28	1.39	1.28	-				
15	1.28	-	1.28					
16	1.18		1.18					
17	1.18		1.18					
18	1.18		1.09					
19	-		1.05					
20			1.00					
21			0.93					
22			0.93					
23			0.85					
24			0.85					
25			0.85					
			-					
Cumulative toxicity factor (acute/chronic)	2.84	2.06	4.01	2.05	21.74	27.99	2.06	2.53

These data are from Lawrence et al. (1975).

Lawrence et al. (1975) also reported that most of the phthalate esters studied (except diisobutyl and possibly diethyl) prolonged pentobarbital-induced sleeping time in mice. These authors also investigated certain other aspects of subtle toxicity.

Rubin and Jaeger (1973) also demonstrated some subtle toxicological effects of di-(2-ethylhexyl) phthalate (DEHP) involving behaviour changes in rats and changes in platelet aggregation in dog blood.

Albro and Thomas (1973) reported that di-(2ethylhexyl) phthalate was hydrolyzed by lipases from a variety of rat tissues. Of the preparations studied only glycerol-ester hydrolase (pancreatic lipase EC 3.I.I.3) and sterol-ester hydrolase (cholesteryl ester hydrolase EC 3.I.I.13) were unable to hydrolyze the phthalate diester. Of 15 different tissue preparations, however, only the liver alkaline lipase preparation could hydrolyze mono-2-ethylhexyl phthalate at a significant rate.

Peakall (1974) studied the effects of di-n-butyl phthalate (DBP) and di-(2-ethylhexyl) phthalate (DEHP) on the eggs of ring doves. The most significant findings were that eggshell thickness was decreased and permeability to water increased by a diet containing 10 ppm of DBP. In contrast, no significant effect was found with DEHP.

Yamada (1974) observed liver enlargement in rats as a result of a three-week administration of 4 to 10 mL/kg day doses of DEHP. After DEHP (5 mL/kg day) was given orally for three weeks the glycogen content of the liver was decreased and the BSP clearance was inhibited but the water, protein, and fat contents of the liver and the activities of alkaline phosphatase, lactate dehydrogenase, glutamate-oxaloacetate transaminase, and glutamate-pyruvate transaminase in the serum showed no differences from the control groups.

Lee et al. (1974) studied the effects of di-(2-ethylhexyl) phthalate, di-(2-butoxyethyl) phthalate, dimethyl phthalate, and diisodecyl phthalate on chick embryos grown in ova and in vitro as well as in cultured chick embryonic cells. Toxic effects resulting in death of embryos were produced by phthalate esters administered in undiluted form, but teratogenic effects were not observed in explanted streak stage embryos or hatched chicks. However, chick Ringer's solution saturated with phthalate esters caused a distinct growth retardation

and produced non-specific malformations, particularly in the central nervous system. These effects appeared to be related to the solubilities of phthalate esters in water. Furthermore, phthalate esters at concentrations of about 0.05 mg/mL or higher were toxic to cultured chick embryonic cells.

Sugawara (1974 a, b) studied the toxic effect of some phthalate esters on the hatching of brine shrimp (Artemia salina) eggs. The toxic order of three phthalates was: dibutyl phthalate > diethyl phthalate > dimethyl phthalate. The water solubility of the phthalates was not related to their toxicity, since in some experiments (Sugawara 1974a) Triton X-100 was added to dissolve the phthalate esters.

Schulz et al. (1975) found that intravenous administration of 200 to 300 mg/kg of di-(2-ethylhexyl) phthalate (DEHP) dissolved in aqueous solutions of several Tween surfactants caused respiratory distress in rats. There was a dose-dependant lethality with death generally occurring withing 90 minutes after injection. The lungs from DEHP:Tween-treated animals were enlarged, generally darkened, and in some cases showed hemorrhagic congestion. At doses of 200 mg/kg and above, the ratios of wet lung weight to body weight for rats treated with DEHP:Tween were significantly elevated over those for vehicle-injected or noninjected controls. Histological examination of lungs from DEHP: Tween 80-treated rats revealed an edematous swelling of the alveolar wall and a marked infiltration of polymorphonuclear leukocytes. These effects were evident at doses as low as 50 mg/kg. Neither the overt signs nor the morphologic alterations resulting from DEHP:Tween administration could be reproduced by intravenous administration of aqueous Tween solutions alone. The absence of pulmonary abnormalities following the intravenous administration of DEHP as an aqueous emulsion given either alone or even as soon as two minutes after pretreatment with Tween 80, suggested that the specific in vivo interaction between DEHP and Tween surfactants depended on the prior formation of water-soluble micelles of DEHP.

Rubin (1976) reported that DEHP dissolved in polyethylene glycol 400 or Emulphor 620 also produced an inflammatory response of the pulmonary tissue, lung toxicity and often death in rats. The pathology was highly suggestive of the syndrome referred to as shock lung. The effects were independent of the type of surfactant used and they appeared to be due only to solubilization of the normally water-insoluble DEHP.

Lee et al. (1977) studied the effects of commercially available di-(ethylhexyl) phthalate on the development of three-day old chick embryos. At the volume of 0.05 mL of DEHP per embryo the ester was highly toxic but it produced neither specific malformations nor apparent changes in serum proteins. The most conspicuous change in affected embryos was the degeneration of extraembryonic blood vessels.

Seth et al. (1977) studied the effect of DEHP on the biological action of two sedative-hypnotics. They found that DEHP prolonged the sleeping time induced by either pentabarbitone or methaqualone in both rats and mice.

Kevy (1978) has recently reported abnormalities in liver histopathology and liver function in rhesus monkeys transfused with blood components which contained DEHP and silicon due to storage in polyvinyl chloride (PVC) and siliconized glass. The abnormalities were demonstrated by compartmental analysis of BSP kinetics and $^{99}TC^{m}$ liver-spleen scans for up to 14 months following the cessation of transfusions. Silicon and DEHP persisted in the liver biopsy specimens throughout this time period.

Pfuderer and his co-workers have found that dibutyl phthalate and possibly some other phthalates but not di-(2-ethylhexyl) phthalate are heart rate depressors in goldfish (Pfuderer and Francis, 1975) and in cyprinodont fish (Pfuderer et. al., 1975).

Seth et al. (1976) studied the effect of di-(2-ethylhexyl) phthalate (DEHP) on rat gonads. The activities of succinic dehydrogenase and adenosine triphosphatase were significantly reduced and the activity of β-glucuronidase was increased in rat gonads after treatment with DEHP. Histopathological studies revealed focal degeneration of seminiferous tubules and edema of intersitium in testis but no detectable alterations in ovary of treated animals as compared to controls. The authors suggested that such alterations might be responsible for the reported reproductive dysfunction in experimental animals after exposure to this and other phthalate plasticizers.

Cater et al. (1977) found that daily oral administration of dibutyl phthalate (DBP) at 2 g/kg for four days to young male rats produced testicular injury and loss in organ weight. Additionally, it was found that DBP treatment adversely affected zinc metabolism. The urinary excretion of zinc was increased

and the zinc content in the testes was markedly decreased. Moreover, the turnover rate of this element in testicular tissue was substantially enhanced. DBP treatment did not significantly alter the zinc concentrations in the kidney and liver. Investigations using n-butanol, phthalic acid and monobutyl phthalate (MBP), the major metabolite of DBP, showed that testicular effects were reproducible by MBP. Coadministration of zinc was found to afford a substantial measure of protection against testicular damage produced by DBP.

10. Interactions and synergistic effects

It appears that interactions of phthalate esters with each other and with other substances and any possible synergistic effects have not been investigated.

F. HUMAN HEALTH EFFECTS

1. Metabolism

According to Autian (1973), phthalate esters can be absorbed from the intestinal tract, intraperitoneal cavity and lungs.

Rubin and Schiffer (1976; Rubin, 1976) studied the disappearance of di-(2-ethylhexyl) phthalate (DEHP) from human blood in six leukemic patients who had received DEHP-contaminated transfusions of blood platelets. The concentrations of DEHP fell exponentially at a mean rate of 2.83 $\pm$ 0.45 percent per minute and had a mean half-life of 28.0 $\pm$ 4.3 minutes.

Jaeger and Rubin (1973 b) measured the DEHP content of human tissues after autopsy from patients who had received DEHP from transfusions or from hemodialysis. Some but not all patients had measurable amounts of DEHP in their body tissues. Jaeger and Rubin (1973b) also detected phthalic acid in the urine of three normal adult males as well as in a transfused patient.

Lake et al. (1977) made a study of the in vitro hydrolysis of dimethyl, diethyl, di-n-butyl, di-n-octyl, di-(2-ethylhexyl), and dicyclohexyl phthalates by both hepatic and intestinal preparations from various species. Hepatic preparations from the rat, baboon and ferret hydrolyzed each of the phthalate diesters to their corresponding monester derivatives. Additionally, intestinal preparations from the three animal species and from man also catalyzed the monohydrolysis of phthalate diesters. These results thus showed a species similarity in the metabolism of phthalate diesters between man, a rodent, a

nonrodent, and a nonhuman primate species. Furthermore, the results suggested that orally ingested phthalate diesters would most probably be absorbed from the gut of the rat, baboon, ferret, and man primarily as the coresponding monester derivatives.

Rock et al. (1978) followed the accumulation of di-(2-ethylhexyl) phthalate (DEHP) and one of its major metabolites, mono-2-ethylhexyl phthalate (MEHP) during storage of whole blood, platelet-rich plasma, platelet concentrates, and platelet-poor plasma for periods ranging from 72 hours to four weeks. Both phthalates showed a progressive increase in concentration with time. While the levels of DEHP were much greater than those of MEHP, there was nonetheless a significant and continuous increase in MEHP in all preparations. The highest concentrations of both DEHP and MEHP were found in the platelet-poor plasma, indicating that platelets do not have a major role in the accumulation of the phthalates in blood. The accumulation of MEHP was shown to be a direct result of the metabolism of DEHP by plasma protein(s) rather than leaching from the blood bag.

2. Essentiality and biological role

There appears to be no evidence that phthalate esters are in any way essential for human nutrition or that they have any particular biological role.

3. Acute toxicity

Three cases of ingestion of phthalate esters by adult human males have been reported (Krauskopf, 1973). A 5 g dose of di-(2-ethylhexyl) phthalate produced no detectable effects; a 10 g dose resulted in diarrhea. With dibutyl phthalate, a 10 g single dose caused nausea, vertigo, keratitis, and toxic nephritis. Tepper (1973) noted that human oral toxicity cannot be judged on the basis of three single doses of 5 or 10 mL (sic) of DEHP taken by volunteers or in error.

4. Mutagenesis

Jones et al. (1975) found that di-(2-ethylhexyl) phthalate and butyl glycolyl butyl phthalate cause significant growth inhibition in cultures of the human WI-38 diploid cell. Values of ID_{50} (the media concentrations which cause 50 percent growth inhibition in tissue culture) for various phthalates using WI-38 cells were calculated in concentration units of micromoles per litre as follows: butyl glycolyl butyl phthalate, 12; di-(2-ethylhexyl) phthalate, 70;

di-iso-butyl phthalate, 85; di-n-butyl phthalate, 135; di-n-octyl phthalate, 170; and dimethoxyethyl phthalate, 3500. Toxic effects were greater in a replicating cell population than in a non replicating, confluent cell layer. WI-38 cells which were grown in 160 micro Molar di-2-ethylhexyl phthalate for 3 days, and subsequently subcultured into control medium, showed only 60 percent of control growth after 5 days in control medium. Cells treated with 14 micro Molar butyl glycolyl butyl phthalate for 3 or 5 days exhibited growth equivalent to the controls when subcultured into control medium. Toxic levels for di-2-ethylhexyl phthalate were within the range of concentrations found in blood which had been stored in polyvinyl chloride blood bags for up to 21 days at 4°C.

Tsuchiya and Hattori (1976) reported that dimethyl-, diethyl-, dibutyl-, and di-(2-ethylhexyl) phthalates at concentrations of 0.25 mg/mL had no effect on chromatid aberration in human leukocyte cultures compared to controls.

5. Other possible effects

It appears that there have been no epidemiological or other studies which indicate that phthalate esters might be carcinogenic, teratogenic or allergenic to humans.

Men'shikova (1971) determined the olfactory threshold of dibutyl phthalate for 19 humans, aged 17 to 42. The minimum perceptible concentrations varied widely, from 0.26 to 1.47 mg/m^3. The threshold was found to be 0.26 mg/m^3 for the more sensitive subjects. The maximum imperceptible (subliminal) concentration was 0.16 mg/m^3. She recommended that the concentration of dibutyl phthalate in the air of shipboard quarters should not exceed 0.1 mg/m^3 and also that the one-time and mean diurnal permissible concentrations of dibutyl phthalate in outdoor air should be 0.1 mg/m^3.

II. EVALUATION AND ASSESSMENT

II. EVALUATION AND ASSESSMENT

A. EXPOSURE ASPECTS

1. Calculated acceptable doses

The no-effect levels observed in the chronic feeding studies summarized in Table 38 (Section I.E.9) for di-(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate and heptyl nonyl phthalate of 60, 110 and 60 mg/kg day, respectively, provide the best currently available bases for calculating acceptable daily intakes (ADIs) for humans. In view of the possible teratogenic properties of phthalate esters (Singh et al., 1972) it is prudent to apply a safety factor of 500. Thus, for an average adult human weighing 70 kg the ADIs are 8.4, 15.4 and 8.4 mg/day for DEHP, dibutyl phthalate and heptyl nonyl phthalate, respectively.

When exposure to any phthalate or a combination of a number of phthalates occurs, there should be no adverse effects provided that the total daily intake does not exceed 8.4 mg.

2. Other published recommendations or opinions

According to Hugos (1972 a) and Peakall (1975) maximum permissible concentrations in drinking water of dibutyl phthalate (2 mg/L, based on its toxicity) and dioctyl phthalate (2.5 mg/L, based on its odour) were recommended by Maslenko (1967, 1968, 1969). Men'shikova (1971) recommended that the concentration of dibutyl phthalate in the air of shipboard quarters should not exceed 0.1 mg/m^3 and also that the one-time and mean diurnal permissible concentrations of dibutyl phthalate in outdoor air should be 0.1 mg/m^3

Threshold limit values (TLVs®) for various phthalate esters and phthalic anhydride in the workroom environment have been adopted by the American Conference of Governmental Industrial Hygienists (ACGIH). In 1972 the TLVs for dimethyl, dibutyl, and di-(2-ethylhexyl) phthalates were set at 5 mg/m^3 (Anon., 1972 a; Peakall, 1975).

B. CURRENT EXPOSURE LEVELS

1. From food, air and water

About 800 g of the total daily diet of a man, which is about 1780 g (Kirkpatrick and Coffin, 1974), would consist of fatty foods, which are likely to contain phthalate esters. Although there is a lack of comprehensive data regarding phthalate ester concentrations in the diet, it is possible to make

certain assumptions based on measured concentrations. Leah (1977) assumed that fatty foods contain phthalates at about 0.1 µg/g, the order of magnitude of phthalate concentrations found by Williams (1973) in fish. To make a worst-case estimate, Wei et al. (1978) assumed the phthalate levels in such fatty foods to be the same as those found by Williams (1973) in the most contaminated fish samples available to the Canadian consumer, 0.24 µg/g on a wet weight basis. Thus, Leah (1977) estimated the total daily intake by a man of phthalate esters from food as about 80 µg but Wei et al. (1978) suggested that it might be as high as 192 µg.

Assuming an ambient concentration of phthalate esters in air of 1 $\mu g/m^3$, which is slightly higher than the highest reported atmospheric level in Canada (Thomas, 1973), and also assuming that the volume of air breathed per day is 15 (Anon., 1973 c) to 20 m^3 (Wei et al., 1978), the daily intake by a man of phthalate esters from respiration has been estimated as 15 to 20 µg.

Phthalate esters were not detected in 41 of 80 drinking water samples from water treatment plants in Ontario but the other 30 samples were found to contain phthalates at concentrations which ranged from 0.05 to 9.0 µg/L, with most of these samples containing less than 1 or 2 µg/L (Meresz, 1977 a).

The average adult man's intake of water-based fluids may be assumed to be about 2 litres per day. Assuming a worst case, where all drinking water contains phthalate esters at a concentration of 9.0 µg/L, the highest concentration found in Ontario, the maximum daily intake of phthalates from water would be approximately 18 µg.

Thus, on the basis of a worst-case estimate for the general population, the maximum daily intake of phthalate esters by man from food, air and water would be 230 µg or 0.23 mg.

2. Special situations of exposure

There are additional sources of phthalate esters for certain population groups such as industrial workers who manufacture or process phthalates and some medical patients who are exposed to di-(2-ethylhexyl) phthalate (DEHP) from blood transfusions, hemodialysis and intravenous feeding, due to the presence of this ester in blood bags and PVC tubing. The levels of certain phthalate esters in some drinking water supplies may be elevated if PVC sheeting is used for lining potable water storage tanks. Data to support this hypothesis are sparce and the extent of such applications is unknown.

C. ASSESSMENT OF RISK

The maximum probable daily intake of phthalate esters by an average person, 0.23 mg (from Section II.B.1), which is a worst-case estimate, is less than the estimated acceptable daily intake (ADI) of 8.4 mg (from Section II.A.1) by a factor greater than 36.5. It seems, therefore, that there is at present no significant risk to the general population from phthalate esters.*

Observations made by the authors of some review articles support this conclusion. According to Autian (1973) the small amount of information available from chronic toxicity studies and human experience of a quarter of a century of use suggest an extremely low toxic potential of diethyl phthalate. On the basis of data available in 1973, Dernehl (1973) concluded that there "was no hazard to humans from ingestion of phthalates at present use levels".

The highest atmospheric concentration of phthalate esters in Canada, reported by Thomas (1973), of nearly 1 $\mu g/m^3$ (see Sections I.D.1.c and II.B.1) is a factor of 100 lower than at the maximum permissible concentration recommended by Men'shikova (1971) for dibutyl phthalate in air of 0.1 mg/m^3 (see Section II.A.2).

The highest concentrations of phthalate esters in Canadian drinking water (between 5.0 and 9.0 µg/L) reported by Meresz (1977 a) (see Sections I.D.1.a and II.B.1) are evidently well below the maximum permissible concentrations in water of dibutyl phthalate (2 mg/L) and dioctyl phthalate (2.5 mg/L) recommended by Maslenko (1967, 1968 and 1969) (See Section II.A.2).

* Note added in press: The results of a two-year study conducted by the United States National Cancer Institute, which were released recently by the U.S. Environmental Protection Agency, were interpreted as showing that di-(2-ethylhexyl) phthalate caused liver cancer in rats and mice. Currently, these results are being evaluated by staff of the Health Protection Branch, Department of National Health and Welfare; if the findings are confirmed, reappraisal of the health risks associated with exposure to phthalic acid esters may be warranted.

III. RESEARCH NEEDS

III. RESEARCH NEEDS

If the use of phthalate esters continues to increase it will be desirable to periodically determine the extent to which the populace becomes exposed. Phthalate levels in water, air, food and biological tissues should then be collected.

Further studies to more fully understand the fate of phthalate esters in the environment (incuding measurement of the rates of degradation and identification of the degradation products) are desirable.

Further and more detailed studies of chronic toxicity are needed to determine the low level, long-term effects of phthalate esters on humans, resulting from oral ingestion or other types of exposure. From such studies it should be possible to establish more precise no-effect levels. Many no-effect levels have been reported but there has been considerable variation in such levels observed by different scientists for various species.

The importance of teratogenic and mutagenic effects at current environmental levels, as well as at excessively high doses, remains to be assessed.

IV. EXISTING REGULATIONS

IV. EXISTING REGULATIONS

A. IN CANADA

The use of phthalates or other possibly injurious substances in food packaging in Canada is controlled under the Food and Drugs Act, Division 23, Section B.23.001, p. 738, February 10, 1976, which states, "No person shall sell any food in a package that may yield to its contents any substance that may be injurious to the health of a consumer of the food".

B. OTHER COUNTRIES

1. In the U.S.A.

Regulations for the use of phthalate esters in food packaging in the United States, which are included in the (U.S.) Code of Federal Regulations, 21. Food and Drugs, January 1, 1972, have been described by Shibko and Blumenthal (1973), and by Shibko (1974).

The regulated uses have been classified into three categories that reflect the possible levels of direct migration to foods; namely, significant, slight, and essentially zero. Table 40 lists regulated uses that could result in migration of phthalates to foods. The uses listed in Table 40 include (a) those that will be major contributors of phthalate migration to foods (for which there must be prior sanction), and (b) those that will result in slight migration to foods. Regulated uses that, under normal conditions, would not be expected to result in migration to foods are listed in Table 41.

Phthalate esters that are regulated for uses that would be expected to result in migration to foods are listed in Table 42. Each ester may have several uses, some of which would result in migration to foods and others which would not. Some phthalate esters are regulated only for uses that would not be expected to result in migration to foods under normal conditions of use (Table 43). In the case of phthalate esters approved by prior sanction, theoretically all the phthalate esters (except those intended for use with foods of a high water content) used in food-packaging material could migrate into fatty foods held for a period of time in the package. The amount available for migration will be limited by good manufacturing practice for food-packaging materials, which includes a restriction that the quantity of the substance used shall be reduced to the least amount reasonably possible.

TABLE 40
Regulated Uses of Phthalate Esters That Could Result in Migration into Foods[a,b]

121.2001	Substances employed in manufacture of food-packaging material (prior sanction)
121.2511	Plasticizers in polymeric substances
121.2514	Resinous and polymeric coatings
121.2526	Components of paper and paperboard in contact with aqueous and fatty foods
121.2550	Closures with sealing gaskets for food containers
121.2531	Surface lubricants used in the manufacture of metallic articles
121.2569	Resinous and polymeric coatings for polyolefin films
121.2507	Cellophane

[a]Code of Federal Regulations 21. Food and Drugs, Jan. 1, 1972.

[b]Order of listing reflects possible level of migration into foods (i.e., 121.2001, 2511, 2514, 2526 and 2550 will result in greatest migration; 121.2531, 2569, 2507, only slight migration).

TABLE 41

Regulated Uses of Phthalate Esters That Under Normal Conditions of Use Would Not Reasonably be Expected to Result in Migration to Foods, Based on Available Scientific Information and Data[a]

121.2577	Pressure-sensitive adhesives
121.2562	Rubber articles intended for repeated use
121.2571	Components of paper and paperboard in contact with dry food
121.2519	Defoaming agents used in the manufacture of paper and paperboard
121.2520	Adhesives

[a]Code of Federal Regulations 21. Food and Drugs. Jan. 1, 1972.

TABLE 42
Phthalate Esters Regulated for Uses That Could Result in Migration to Foods[a]

Diisooctyl phthalate[b]	Di-n-hexyl phthalate
Ethylphthalyl butyl glycolate[b]	Diphenyl phthalate
Di-2-ethylhexyl phthalate[c]	Dibutyl phthalate
Diethyl phthalate[c]	Diisobutyl phthalate
Butylphthalyl butyl glycolate[c]	Diisodecyl phthalate
Butyl benzyl phthalate	Dimethylcyclohexyl phthalate
Dicyclohexyl phthalate	Dihydroxyabietyl phthalate
Castor oil phthalate, hydrogenated	

[a]See Table 1 for regulated uses. Note: esters usually have one or more regulated uses. Most of these esters are also regulated for uses which would not be expected to result in migration to foods.

TABLE 43

Phthalate Esters Regulated for Uses That Under Normal Conditions of Use Would not Reasonably be Expected to Migrate into Foods[a]

Dibutoxyethyl phthalate
Di-2-ethylhexyl hydrophthalate
n-Octyl n-decyl phthalate
Dioctyl phthalate
Butyl octyl phthalate
Dimethyl phthalate
n-Amyl n-decyl phthalate
Methylphthalyl ethyl glycolate

[a]See Table 2 for list of regulated uses.

These data from Tables 40 - 43 are from Shibko and Blumenthal (1973).

The food additive regulations in the U.S.A. for the safe use of plasticizers in flexible vinyl have been discussed by Rutkowski and Scala (1973) and Ingle (1973) has discussed the (U.S.) federal regulations that affect flexible vinyl products, including those which deal with food contact.

2. In Japan

Omori (1976) has briefly reviewed the regulation of phthalate esters by the Japanese Ministry of Health and Welfare. In 1973 test procedures to restrict the migration of phthalate esters and other substances from polyvinyl choride (PVC) containers or packaging material into (I) fats, oils and fatty foodstuffs, (II) liquors, wines and alcoholic beverages, and (III) other foodstuffs, were adopted.

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